Chapter III

Results and Discussion

A. Preparation and Determination of Modified Starches

1. Preparation of Modified Starches

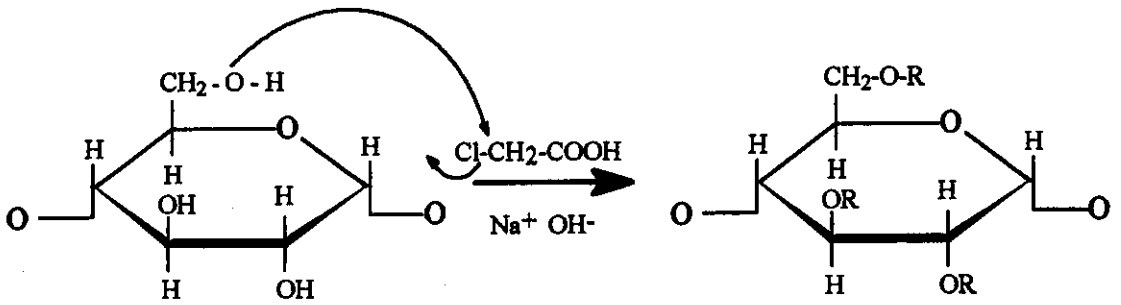
Modified starches were prepared by a carboxymethylation reaction of native starches with monochloroacetic acid in the presence of NaOH as suggested by Filbert (1952). Preparation procedures following the conditions described in Filbert did not yield modified starches with expected DS. The following modification in reaction conditions were made to obtain required products. Modified starches with DS 0.13 were obtained by using Filbert conditions which indicate to have DS 0.23. Modified starches with DS 0.26 were successfully prepared by using Filbert conditions which indicate to have DS 0.34 with the reaction time decreasing from two hours to 20 minutes. Modified starches with DS 0.39 were accomplishedly synthesized by using Filbert conditions which indicate to have DS 0.34. It was found that slight changes in reaction conditions during modification (e.g. temperature, time of reaction) and preparing techniques affected the obtained DS of modified starches (Mishra, Jain, and Agrawal, 1990). The comparative conditions for preparing three degrees of substitution of starch are presented in Table 2.

Table 2 Comparative Conditions for Preparing Three Degree of Substitutions of Modified Starches

Conditions	D.S.		
	0.13	0.26	0.39
g of 100% MeOH	254	-	-
g of 92.4% EtOH	-	286	286
g of MCA	27.6	29.2	29.2
g of 50% NaOH	110	-	-
g of 97% NaOH	-	38.4	38.4
g of Water	-	69	69
g of Starch	109	102	102
Reaction Temperature (°C)	60	50	50
Reaction Time (Minutes)	60	20	120

In the reaction, a water miscible organic solvent was added in order to reduce the formation of alkali gel. This gel formation prevents a uniform reaction of the alkali starch with the etherifying agent (Filbert, 1952). The water miscible organic solvents commonly used are alcohols of the lower aliphatic group such as methanol, ethanol. The preferred reaction temperature is somewhere near the boiling point of alcohol.

The carboxymethyl substitution reaction is shown in Figure 11. The mechanism of this reaction seems to follow SN_2 reaction. NaOH acts as a catalyst. Chloroacetic acid is a strong electrophile for it has chlorine as a good leaving group. There are three reacting positions on one starch unit, i.e. those three -OH group. The number of -OH that was substitued with $-OCH_2-COONa$ or $-OCH_2COOH$ determined the DS of the modified starch.



R = -CH_2-COONa

Figure 11 Reaction Mechanism of the Formation of Sodium Carboxymethyl Starch

2. Determination of a Degree of Substitution (DS)

The degree of substitutions of 12 prepared modified starches (three degrees each of four different starches) were calculated and are presented in Table 3.

From the results in Table 3, the DS of MCS were 0.13, 0.26, 0.39. The DS of MGS were 0.16, 0.26, 0.39. The DS of MRS were 0.15, 0.26, 0.39. The DS of MGS were 0.13, 0.20, 0.38. These values were within ± 0.06 DS unit of their designated DS. The major contribution for the value of DS was from the degree of sodium carboxymethyl substitution (S).

The degree of substitution of modified starches was determined as a summation of degree of acid carboxymethyl substitution (A) and degree of sodium carboxymethyl substitution (S) which were calculated from acid-base titration and residue on ignition experiments (USP XXII). Theoretically, the D.S. value obtained from this calculation represents the carbonyl groups in both acid and salt forms. In this study, however, S value contributes to most of DS value because the reaction takes place in basic

condition. One advantage of modified starches preparing by this method is that their salt form improves solubility in water (Mishra, Jain, and Agrawal, 1990).

Table 3 Calculation of Degree of Substitution of Modified Starches

MCS	0.13	0.0336	5.2900	0.00580	0.12858	0.13438
	0.26	0.0300	9.7700	0.00547	0.25091	0.25638
	0.39	0.0282	14.0400	0.00543	0.38116	0.38660
MGS	0.13	0.0615	6.2000	0.01075	0.15263	0.16338
	0.26	0.0300	10.0000	0.00549	0.25757	0.26305
	0.39	0.0367	14.0100	0.00707	0.38042	0.38749
MRS	0.13	0.0737	5.4200	0.01277	0.13227	0.14504
	0.26	0.0300	9.9600	0.00548	0.25641	0.26189
	0.39	0.0469	14.0000	0.00905	0.38037	0.38941
MTS	0.13	0.0367	5.2300	0.00633	0.12705	0.13338
	0.26	0.0300	7.7800	0.00533	0.19488	0.20022
	0.39	0.0812	13.6200	0.01562	0.36903	0.38465

M = Numbers of Milliequivalent of Base Required to Neutralize 1 gram of Modified Starch

C = Residue on Ignition (%)

A = Degree of Acid Carboxymethyl Substitution

S = Degree of Sodium Carboxymethyl Substitution

A + S = Degree of Substitution

3. Detection of Carboxymethyl Group in Substituted Starches

The infrared spectrograms of native starches and modified starches were shown in Figures 12-17. The carboxymethyl substitution reaction was confirmed by a presence of carbonyl group (C=O) in infrared spectroscopy. C=O peak appeared as a strong broad peak at 1,600-1,650 cm^{-1}. Comparing the IR spectrograms between native and modified starch, the carbonyl peak was clearly more intensive.

B. Evaluation of Modified Starches as Suspending Agents

1. Viscosity Determination

The viscosities of each modified starch at concentration 1, 2, and 3% w/v are shown in Figures 18-21 for MCS, MGS, MRS, and MTS, respectively. The viscosity of all four modified starches increased in accordance with the increasing of concentration used. In Figure 18, the viscosity patterns of MCS were the same in all three concentrations. The decreasing order of viscosity of MCS was DS 0.26 > DS 0.39 > DS 0.13. For 1% and 3% MGS (Figure 19), the viscosity of DS 0.16 > DS 0.26 > DS 0.39 but for 2% MGS the order of viscosity was DS 0.26 > DS 0.16 > DS 0.39. The viscosity patterns of MRS (Figure 20) were the same in all three concentrations. The decreasing order of viscosity of MRS was DS 0.26 > DS 0.15 > DS 0.39. For MTS (Figure 21), the decreasing order of viscosity of MTS was MTS - DS 0.38 > DS 0.20 > DS 0.13.

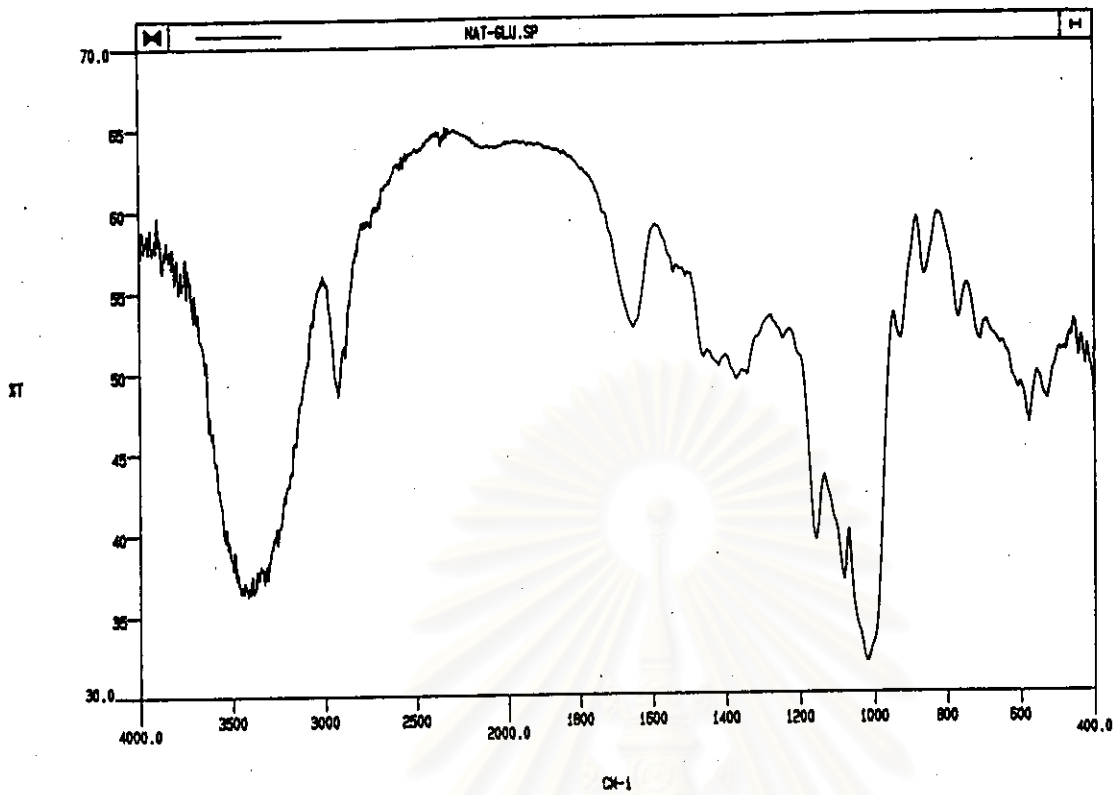


Figure 12 IR Spectrogram of Native Glutinous Rice Starch

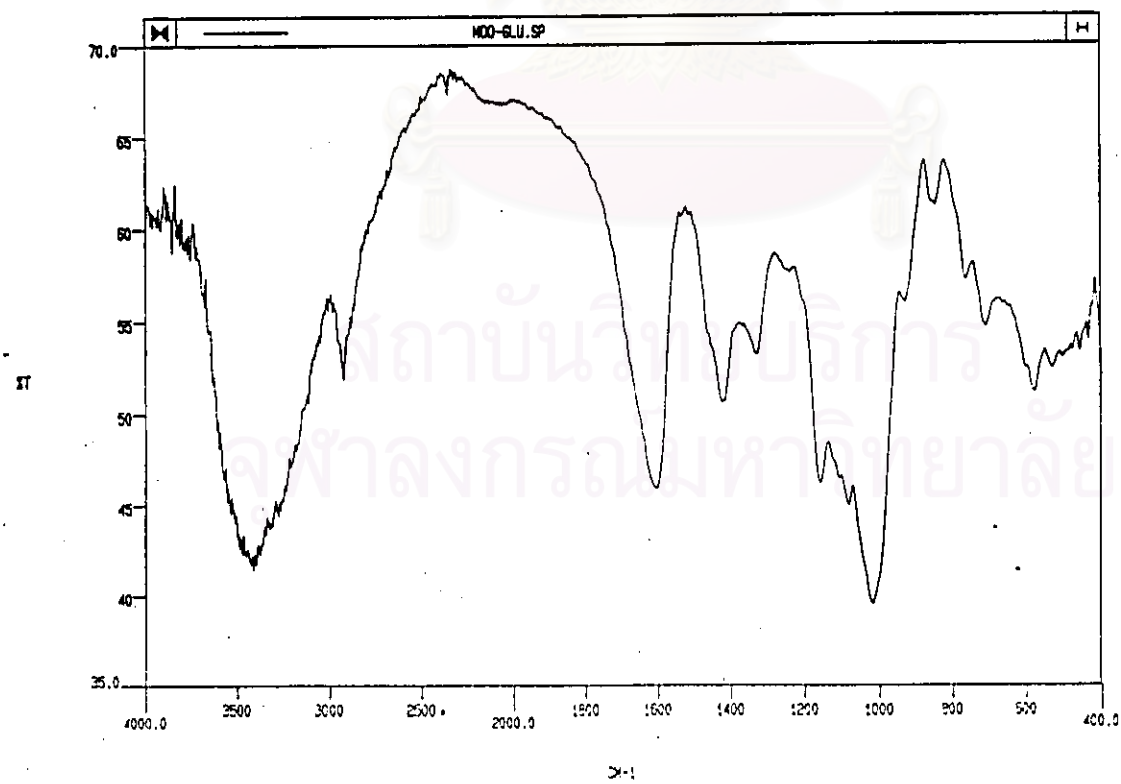


Figure 13 IR Spectrogram of Modified Glutinous Rice Starch

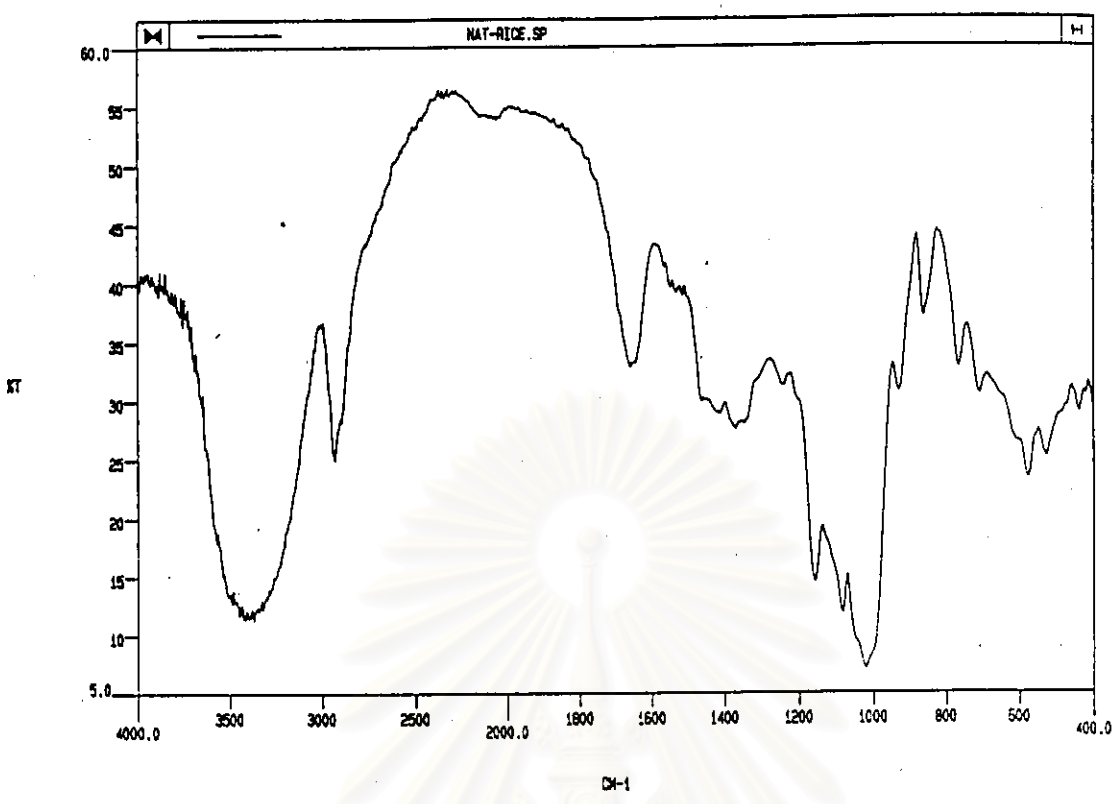


Figure 14 IR Spectrogram of Native Rice Starch

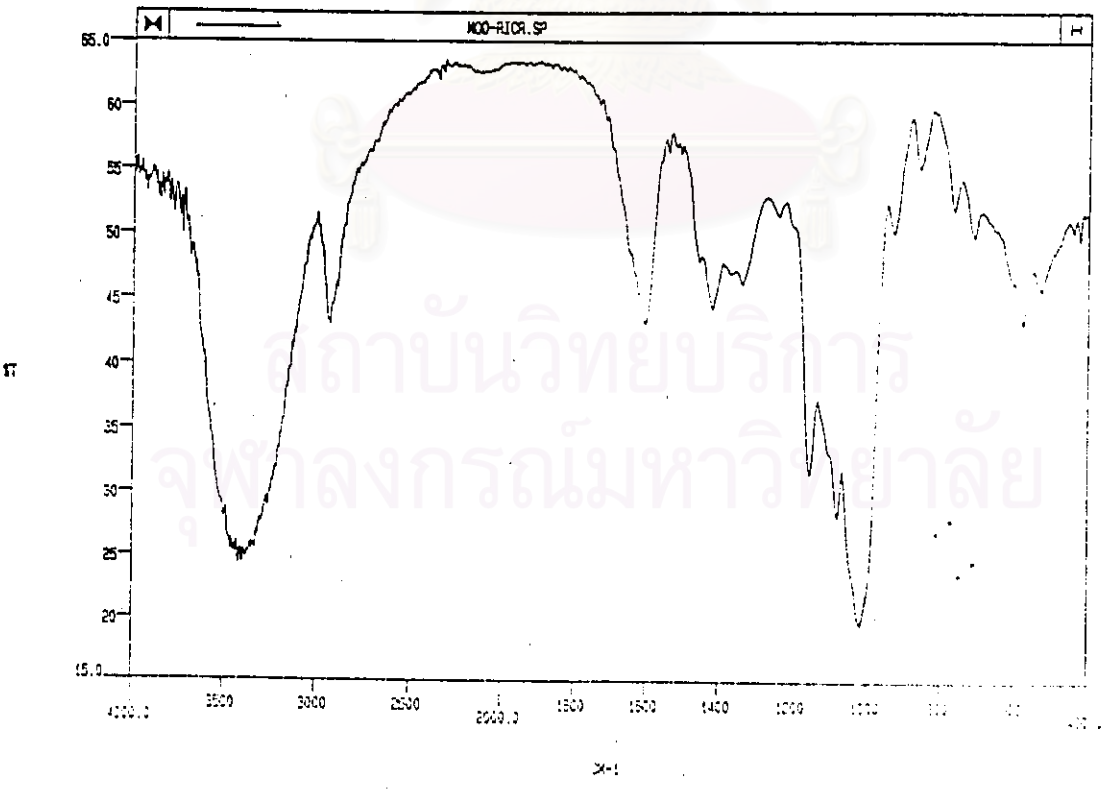


Figure 15 IR Spectrogram of Modified Rice Starch

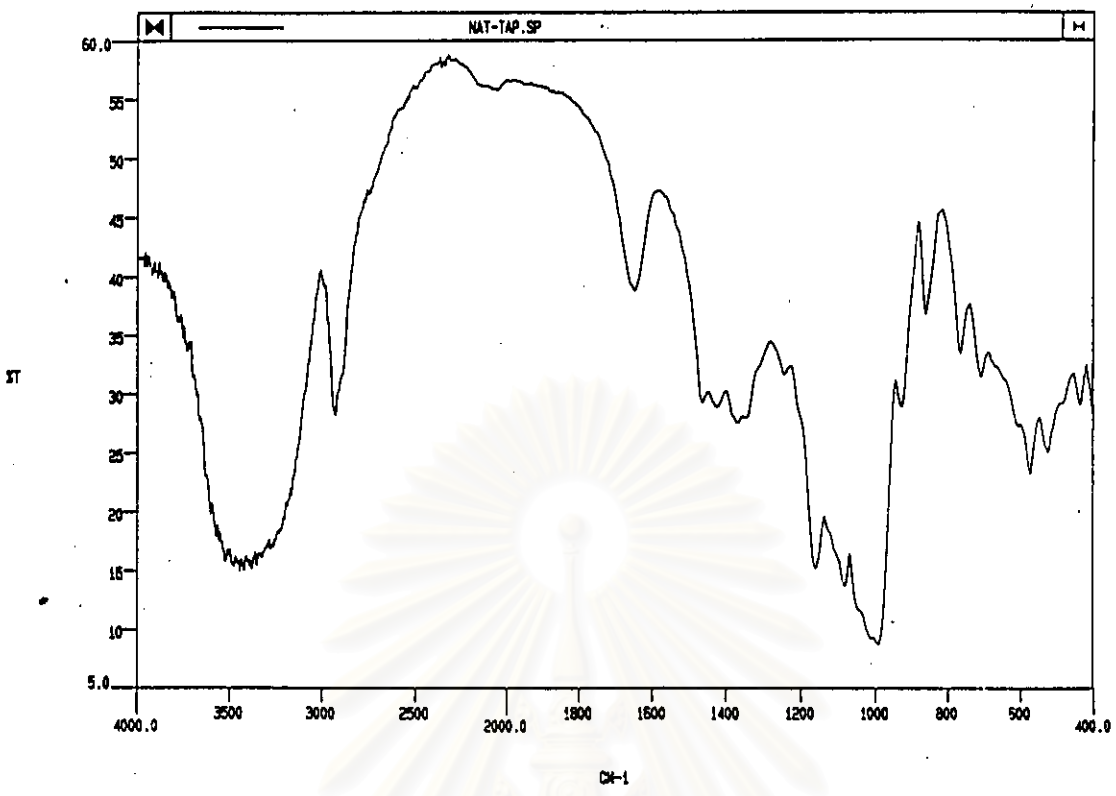


Figure 16 IR Spectrogram of Native Tapioca Starch

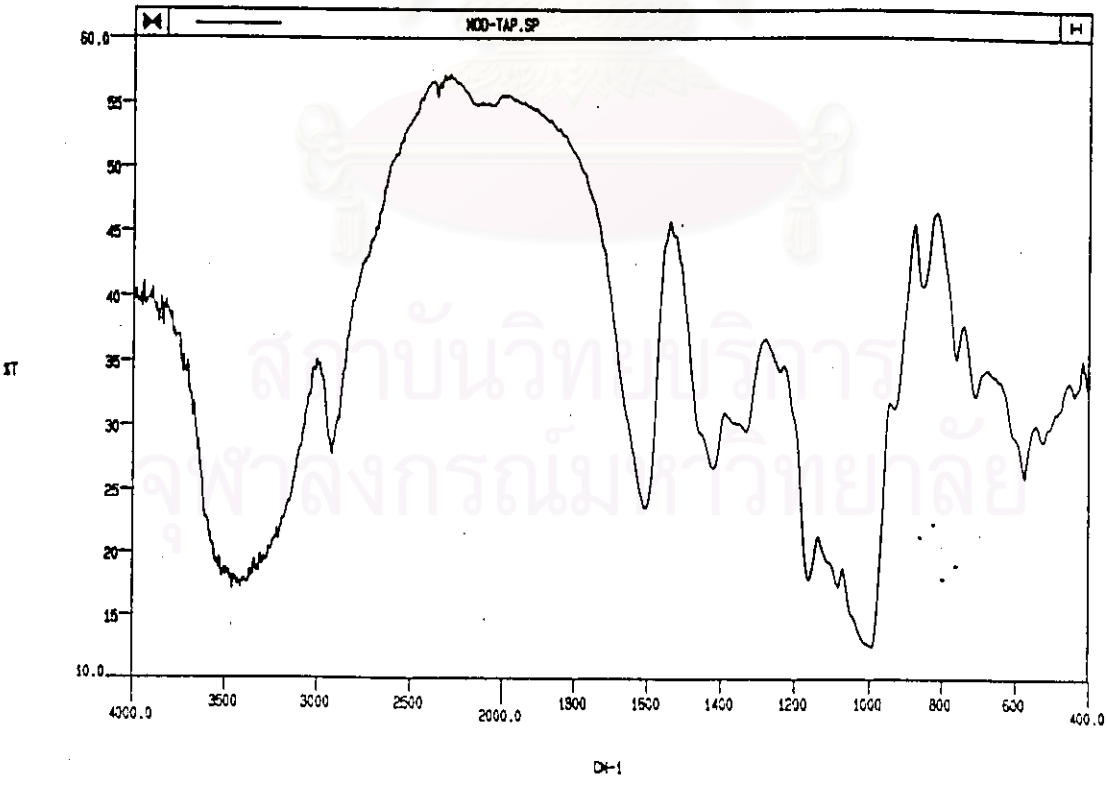


Figure 17 IR Spectrogram of Modified Tapioca Starch

Figure 18 Comparative Viscosity Among Different Degree of Substitution and Concentration of Modified Corn Starch (MCS)

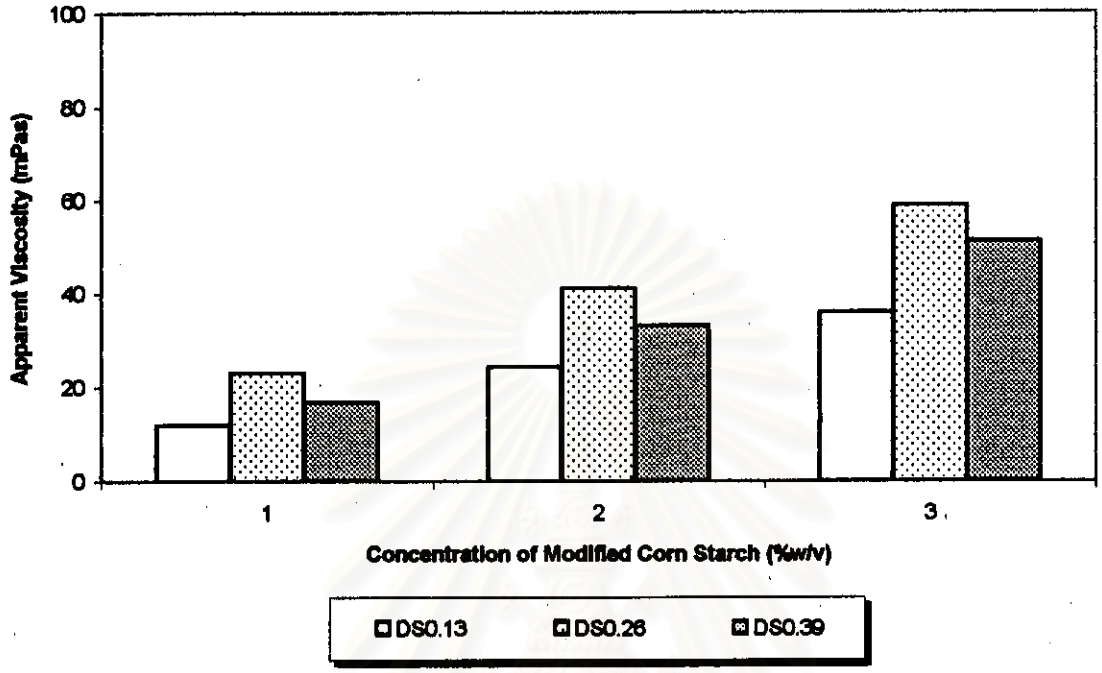


Figure 19 Comparative Viscosity Among Different Degree of Substitution and Concentration of Modified Glutinous Rice Starch (MGS)

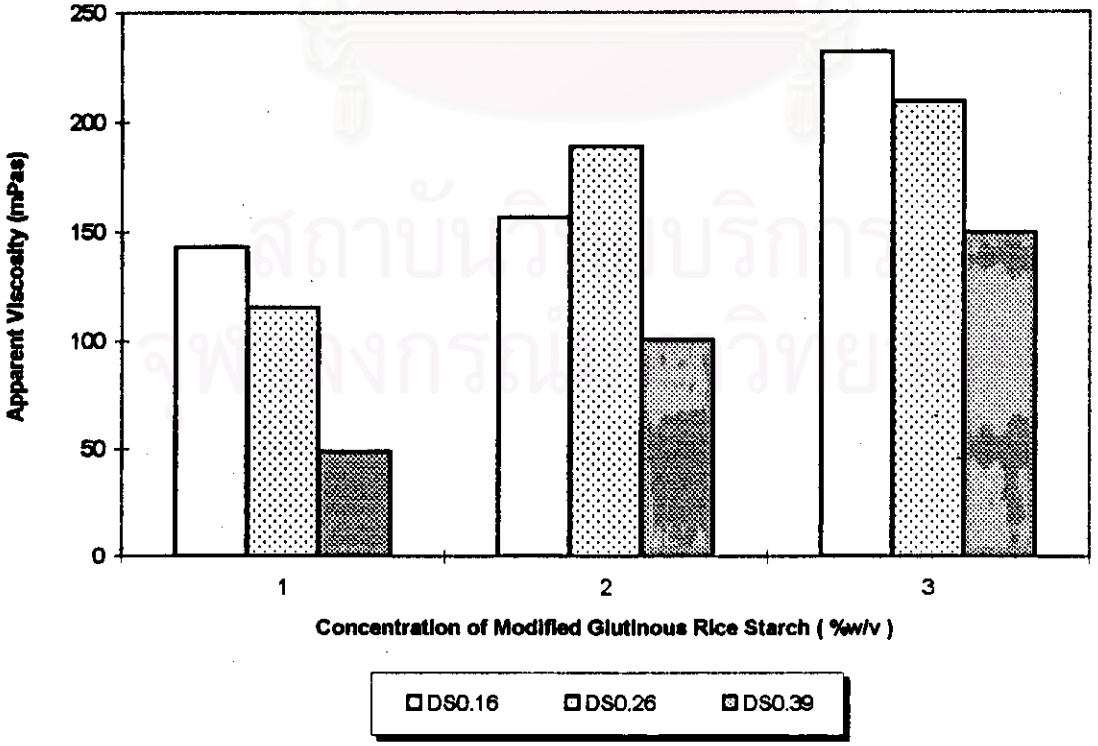


Figure 20 Comparative Viscosity Among Different Degree of Substitution and Concentration of Modified Rice Starch (MRS)

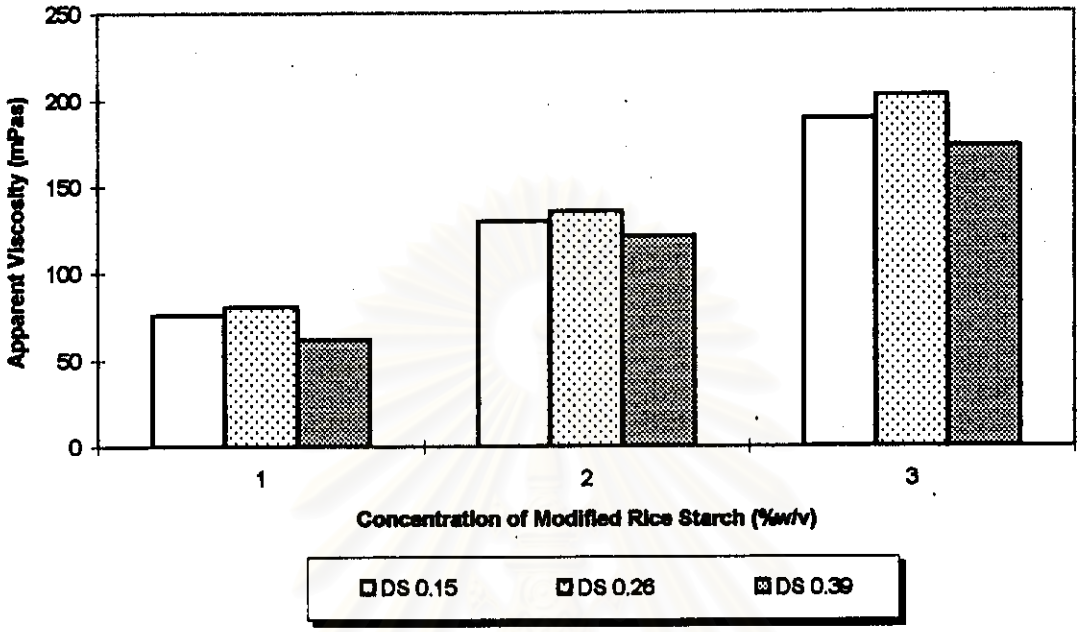
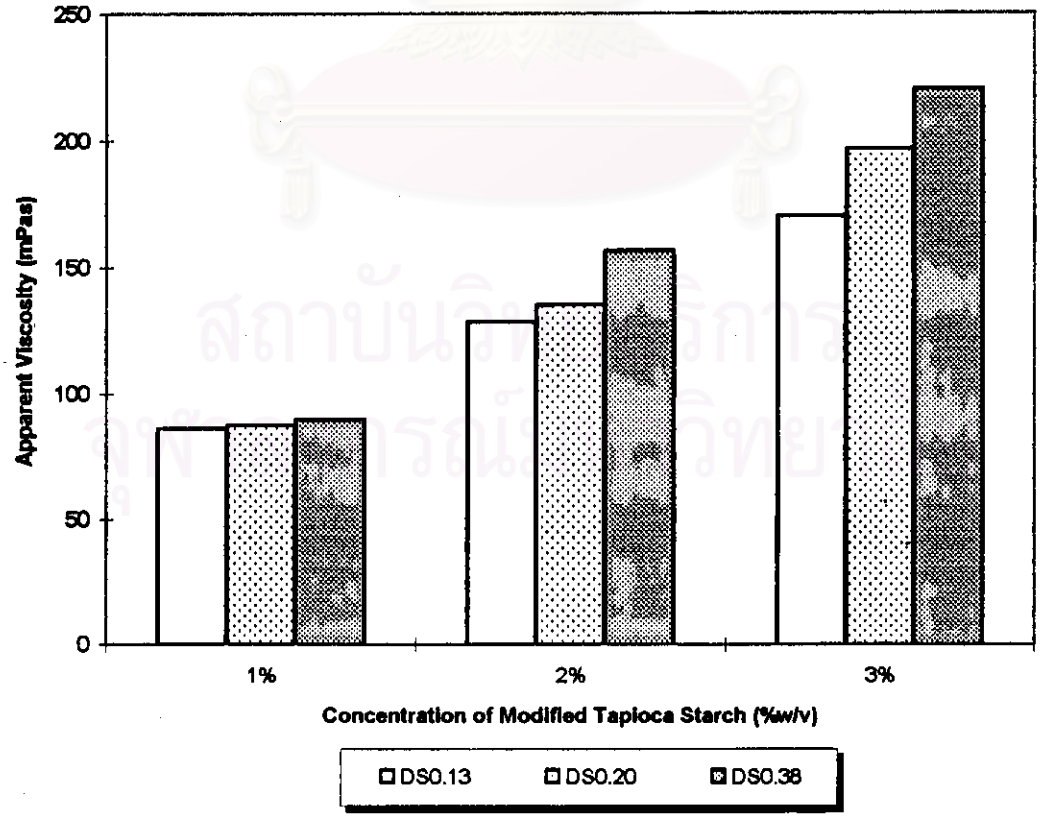


Figure 21 Comparative Viscosity Among Different Degree of Substitution and Concentration of Modified Tapioca Starch (MTS)



The statistical differences ($p < 0.05$) among the viscosity of MS with different DS and concentration are presented in Table 43, 44, 45, and 46 (Appendix II), for MCS, MGS, MRS, and MTS, respectively. The results indicated that there was a significant difference in viscosity among different DS and concentration of each of all modified starches, except for MTS in which the statistical analysis has suggested that no significant difference in viscosity was observed among different DS of MTS ($F = 3.964$, $F_{crit} = 6.944$).

2. Determination of Sedimentation Volume (SV) of $CaCO_3$ Suspensions Containing Modified Starches

The comparative sedimentation volumes (Hu/Ho) of calcium carbonate suspensions are shown in Figures 22-25 for suspensions that contained MCS, MGS, MRS, and MTS, respectively. In Figure 22, all MCS-containing suspensions presented similar decreasing pattern in SV after 2-4 days of settlement. The order of decreasing SV for MCS was DS 0.26 (3%) > DS 0.39 (3%) > DS 0.26 (2%) > DS 0.13 (3%) > DS 0.39 (2%) > DS 0.13 (2%) > DS 0.26 (1%) > DS 0.39 (1%) > DS 0.13 (1%). In figure 23, suspension that contained 1% MGS 0.39 was the only one that possessed SV value lower than 0.50. Other suspensions showed high SV through the first week with the final SV higher than 0.50. Suspensions that contained 3%MGS 0.16 and that contained 3%MGS 0.26 provided the highest SV among all MGS containing suspensions. The order of decreasing SV for MGS was DS 0.16 (3%) = DS 0.26 (3%)

Figure 22 Sedimentation Volume of Calcium Carbonate Suspension Containing Modified Corn Starch as Suspending Agent

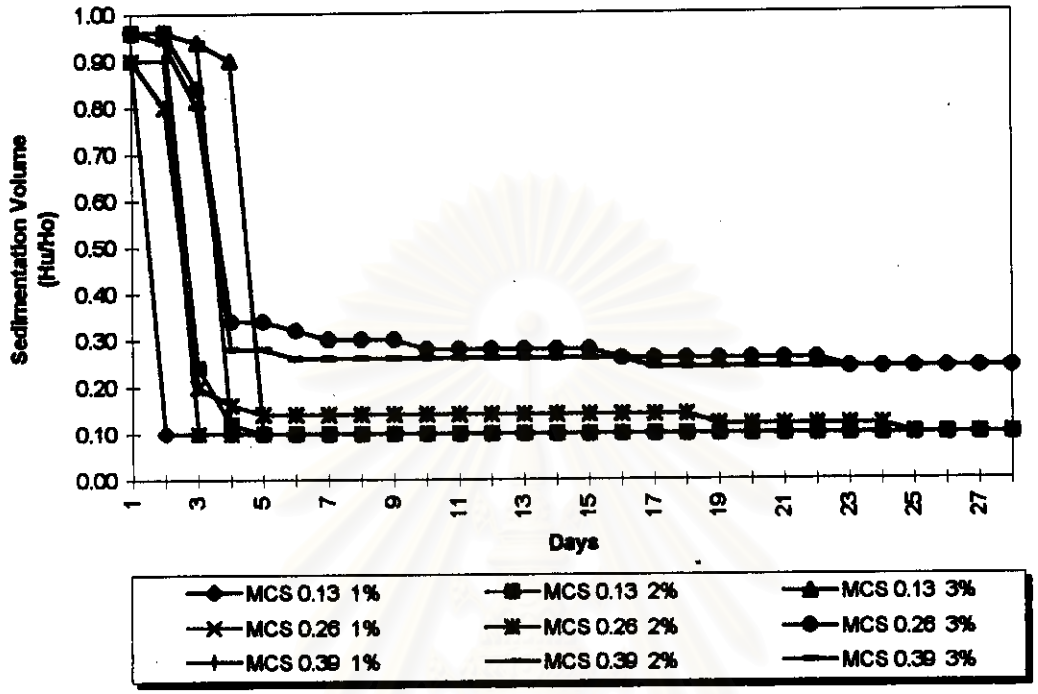


Figure 23 Sedimentation Volume of Calcium Carbonate Suspension Containing Modified Glutinous Rice Starch as Suspending Agent

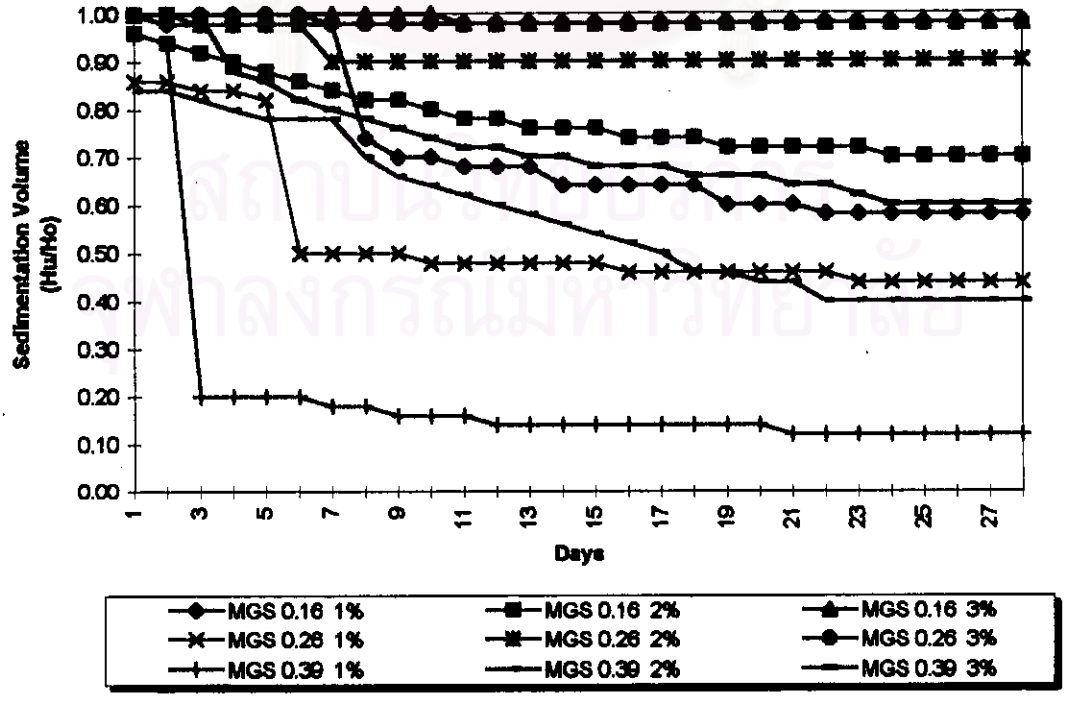


Figure 24 Sedimentation Volume of Calcium Carbonate Suspension Containing Modified Rice Starch as Suspending Agent

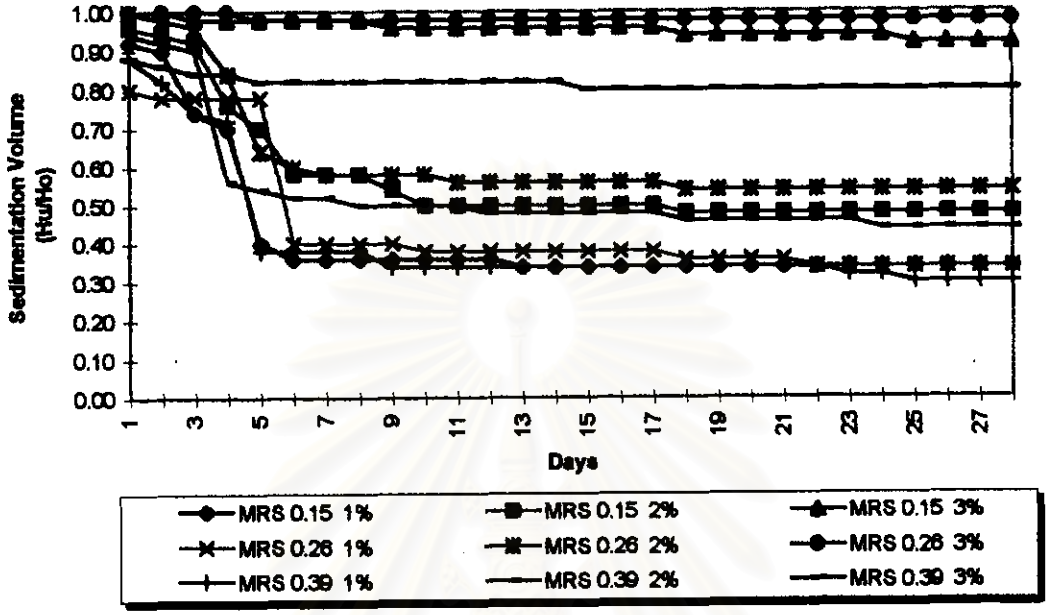
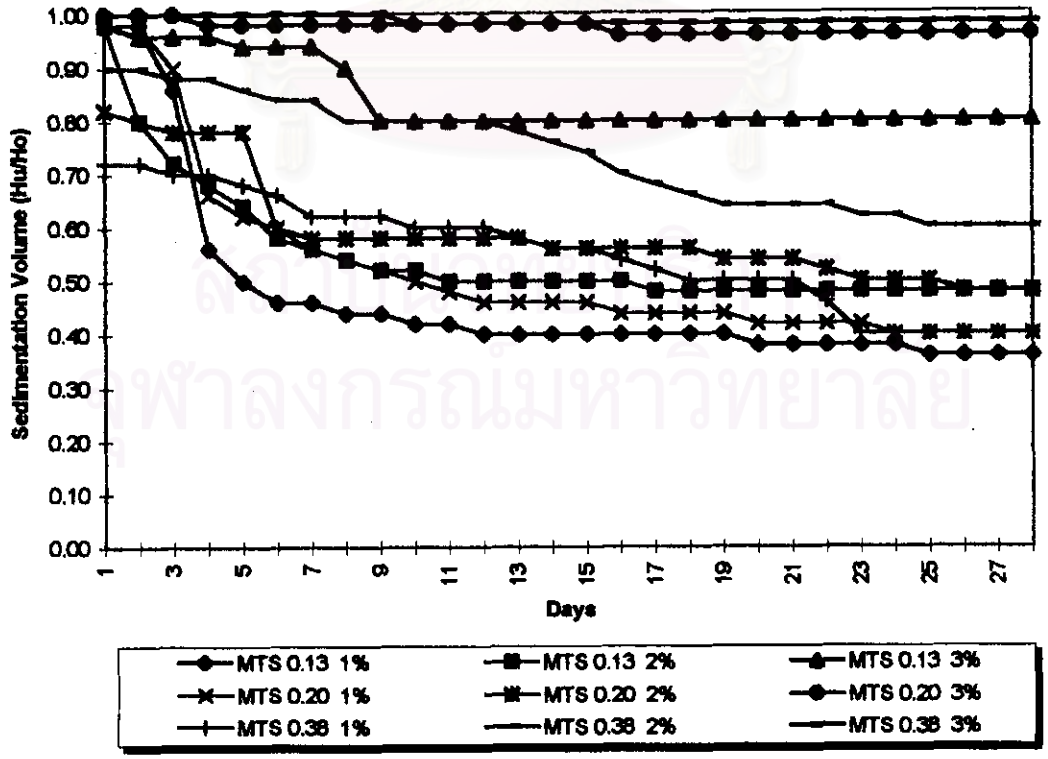


Figure 25 Sedimentation Volume of Calcium Carbonate Suspension Containing Modified Tapioca Starch as Suspending Agent



SV higher than 0.80 in the first three days. After three days, the SV of suspensions that contained 1% and 2% of MRS started to decrease gradually while those contained 3% MRS still maintained their high SV through day 28. The order of decreasing SV for MRS was DS 0.26 (3%) > DS 0.15 (3%) > DS 0.39 (3%) > DS 0.26 (2%) > DS 0.15 (2%) > DS 0.39 (2%) > DS 0.26 (1%) = DS 0.15 (1%) > DS 0.39 (1%). The results of MTS in Figure 25 were similar to those of MRS. The order of decreasing SV for MTS was DS 0.38 (3%) > DS 0.20 (3%) > DS 0.13 (3%) > DS 0.38 (2%) > DS 0.20 (2%) > DS 0.13 (2%) > DS 0.38 (1%) > DS 0.20 (1%) > DS 0.13 (1%).

In summary, SV for modified starches with different DS can be ranked in the following orders of decreasing; for MCS, DS 0.26 > DS 0.39 > DS 0.13; for MGS, DS 0.16 > DS 0.26 > DS 0.39; for MRS, DS 0.26 > DS 0.13 > DS 0.39; for MTS, DS 0.39 > DS 0.26 > DS 0.13. Based on SV, therefore, the best modified starches of each type were MCS DS 0.26, MGS DS 0.16, MRS DS 0.26, MTS DS 0.39.

3. Determination of Redispersibility of Calcium Carbonate Suspension

Redispersibility of calcium carbonate suspensions containing modified starches as suspending agent was evaluated and the results are presented in Table 4 as numbers of inversion required to resuspend such suspensions. The less numbers of inversion required, the better the redispersibility. The results can be interpreted as follows;

For MCS, suspension that contained MCS with DS 0.13 required the lowest number of inversion among all three MCS indicating that its redispersibility was better

Table 4 Numbers of Inversion Required to Redisperse $CaCO_3$ Suspensions

Suspending Agent	%	Week 1	Week 2	Week 3	Week 4
MCS DS 0.13	1	12	12	12	12
	2	3	7	11	12
	3	9	12	vs	vs
MCS DS 0.26	1	vs	vs	vs	vs
	2	vs	vs	vs	vs
	3	10	vs	vs	vs
MCS DS 0.39	1	vs	vs	vs	vs
	2	vs	vs	vs	vs
	3	vs	vs	vs	vs
MGS DS 0.16	1	1	4	4	4
	2	1	3	7	8
	3	0	1	1	1
MGS DS 0.26	1	1	6	7	10
	2	1	4	6	12
	3	0	1	1	1
MGS DS 0.39	1	1	3	5	10
	2	1	1	1	1
	3	1	1	1	1
MRS DS 0.15	1	2	4	6	7
	2	2	4	5	6
	3	2	5	7	9
MRS DS 0.26	1	4	6	7	8
	2	4	5	8	10
	3	4	7	10	12
MRS DS 0.39	1	3	5	6	7
	2	3	5	8	9
	3	3	7	10	11
MTS DS 0.13	1	9	10	12	vs
	2	9	vs	vs	vs
	3	6	vs	vs	vs
MTS DS 0.20	1	5	8	12	12
	2	6	9	9	12
	3	5	9	vs	vs
MTS DS 0.38	1	5	6	6	6
	2	5	7	9	vs
	3	5	8	12	12

vs = vigorously shaken

than the other two. MCS with DS of 0.26 required vigorous shaking in all tests except for the first week of suspension that contained 3% MCS 0.26 in which ten inversions were required. Suspensions that contained MCS with DS of 0.39 required vigorous shaking to achieve redispersibility at all concentration and week of test. The redispersibility of MCS can be ranked as DS 0.13 > DS 0.26 = DS 0.39. In this case, redispersibility decreased when the concentration was increased.

The redispersibility of suspensions that contained MGS was better than other modified starches for they required less number of inversion than any other modified starch. None of MGS-containing suspensions, at any DS and concentration, required vigorous shaking to regain dispersion. For MGS, an increase in concentration used tended to increase redispersibility. The rank of decreasing redispersibility for MGS was DS 0.39 > DS 0.16 > DS 0.26.

Suspensions that contained MRS with DS of 0.15 required lowest number of inversion, among all three MRS, to redisperse the contents. None of MRS-containing suspensions required vigorous shaking. The rank of decreasing redispersibility for MRS was DS 0.15 > DS 0.39 > DS 0.26. In this case, the concentration showed no effect on the redispersibility.

Suspensions that contained 2% and 3% MTS with DS of 0.13 required vigorous shaking after two weeks of evaluation. MTS 0.38 showed the best redispersibility among three MTS with different DS. The rank of decreasing

redispersibility for MTS was DS 0.38 > DS 0.20 > DS 0.13. Like MCS, the increase in concentration of MTS decreased the redispersibility of suspensions.

The results revealed that, among different types of modified starch, suspensions containing MCS required the highest numbers of inversion to regain dispersion. This implied that MCS provided poor redispersibility to the suspension regardless the degree of substitution and the concentration in the formulation. Suspensions containing MTS were somewhat difficult to redisperse and some of them required vigorous shaking before dispersion was achieved. MGS and MRS containing suspensions, on the other hand, were redispersed quite easily. None of these suspensions required vigorous shaking of the tube to regain dispersion. In all cases, the suspensions required equal or more number of inversion as each week proceeded.

According to the results, there was an inconsistency in the relationship between concentration of suspending agent used in the formulation and the redispersibility. It is unclear whether higher concentration of suspending agent provided better redispersibility. For example, in all three DS of MGS, the redispersibility improved when the concentration of suspending agent was increased. In contrast, the redispersibility of MRS, at any DS, was approximately the same at any concentration used. While in MTS, redispersibility decreased when the concentration was increased.

4. Selection of Modified Starch

Preliminary selection of modified starches was made based on the results obtained from three basic suspending properties i.e.; viscosity of pure modified starches and sedimentation volume and redispersibility of calcium carbonate suspension containing modified starches as suspending agent. One starch from each type was selected from three degree of substitution of each starch being prepared. The summary of preliminary evaluations was shown in Table 5-8. In each property evaluation, a rank of 1, 2 or 3 was issued to each DS of modified starch. Modified starch that showed the best result among the three DS was given rank 1 while the one that possessed the poorest result was given rank 3. The selection of modified starch of each type was made based on the obtained ranks of three evaluated properties.

Among three MGS, MGS with DS 0.16 was ranked first in viscosity and SV and was ranked second in redispersibility. It was therefore selected over MGS with DS 0.26, which was ranked second in viscosity and SV, to represent MGS in further evaluations. MGS with DS of 0.39 was not selected because its poorest viscosity and SV, although it was ranked first in redispersibility. For MRS selection, MRS with DS of 0.26 was ranked first in viscosity and SV but was ranked third in redispersibility. Its appropriateness to represent the group was challenged by MRS with DS of 0.15 which was ranked second in both viscosity and SV and ranked first in redispersibility. In this study, MRS with DS of 0.26 was selected because its higher viscosity and better SV than that with DS of 0.15 and also because that its redispersibility, although ranked third, was not much worse than that of DS of 0.15 which was ranked first. MTS with

Table 5 Selection of Modified Corn Starch

Parameter	Rank No.		
	DS 0.13	DS 0.26	DS 0.39
Viscosity	3	1	2
Sedimentation Volume	3	1	2
Redispersibility	1	2	3

Table 6 Selection of Modified Glutinous Rice Starch

Parameter	Rank No.		
	DS 0.16	DS 0.26	DS 0.39
Viscosity	1	2	3
Sedimentation Volume	1	2	3
Redispersibility	2	3	1

Table 7 Selection of Modified Rice Starch

Parameter	Rank No.		
	DS 0.15	DS 0.26	DS 0.39
Viscosity	2	1	3
Sedimentation Volume	2	1	3
Redispersibility	1	3	2

Table 8 Selection of Modified Tapioca Starch

Parameter	Rank No.		
	DS 0.13	DS 0.26	DS 0.38
Viscosity	3	2	1
Sedimentation Volume	3	2	1
Redispersibility	3	2	1

DS of 0.39 was ranked first in all categories of evaluation. It was unanimously selected to represent MTS in further studies.

MCS with DS of 0.26 was ranked first in viscosity and SV and was ranked second in redeispersibility. It was, for a moment, selected to represent MCS in further studies over MCS with DS of 0.39, which was ranked second in viscosity and SV and was ranked third in redispersibility, and MCS with DS of 0.13, which was ranked third in viscosity and SV and was ranked first in redispersiblity. However, MCS possessed poor properties compared to other modified starches. The viscosity of selected MCS was only 20-60 mPas while that of selected MGS, MRS, and MTS were 140-240 mPas, 75-210 mPas, and 90-220 mPas, respectively. In addition, the SV of MCS was so poor that the value was as low as 0.30 within the first week. The suspensions that contained MCS as suspending agent also required several times of inversions to resuspend the content, indicating the poor redispersibility. MCS was, therefore, discarded from further studies.

In summary, MGS, MRS, and MTS being selected for further studies were those with DS of 0.16, 0.26, and 0.38, respectively. MCS was discarded from the study due to its poor suspending properties.

The results from suspending property evaluation of modified starch indicated a strong correlation between viscosity and SV i.e.; suspending agent with high viscosity also possessed fairly good SV, at any concentration used. This is due to the colloid-

supporting property of viscous substances. Highly viscous substance allowed less content to sediment which results in high SV. The results also suggested that modified starches with high viscosity usually exhibited appropriate suspending property and that an increasing in concentration of modified starch would increase the viscosity. Redispersibility property show only little correlation with the viscosity although some results suggested that high viscosity prevented the contents from sedimentation and therefore enhanced the redispersibility. In addition, the relationship between the concentration of modified starches and the redispersibility was inconsistent. The difference in composition and molecular structure among different starches might play a role in this inconsistency.

Considering the modified starches that were selected from each group, the results obviously indicated that there was no relationship between the DS of modified starches and their appropriate suspending properties. For example, MGS with low DS possessed the highest viscosity while in MTS the highest viscosity was found in high DS modified starch. The inconsistency in appropriate degree of substitution among modified starches can be explained by considering the water solubility of each modified starch. Native starches are almost insoluble in water and did not form dispersion. Modification of starch molecules by substituting -OH groups with carboxymethyl groups would increase water solubility of starch molecules (Mishra et al, 1990). At low DS, a little increase in solubility enhances starch molecule to swell and forms a dispersion, therefore the viscosity of the solution increases. As the DS is raised, the viscosity increases. Modified starch exhibits its highest viscosity at a "critical" DS

where the increased solubility results in a fully swelling of modified starch molecule. Beyond this "critical" DS, the solubility of modified starch will be too great that the water molecule breaks apart the bonding network among starch molecules. As a result, the viscosity subsides. The difference in the solubility patterns of each modified starch suggested that critical DS of each modified starch might be a unique characteristic that depend on several factors, i.e.; amylose/amylopectin ratio, molecular structure, modification method, water content, etc.

The highest viscosity value among selected modified starches was observed from MGS. This result suggested that amylose/amylopectin ratio of starch might play an important role in determining the viscosity of modified starch product. Native glutinous rice is sticky because its starch contains low content (0-5%) of amylose (อรวรรณ ทัศน์สองชั้น, 2529) while high amylose content in native corn starch (22-28%) made its modified starch inappropriate as suspending agent. This is in agreement with the study of Schwartz and Zelinskie (1978) which reported that the binding property of starch was due to amylopectin fraction while the disintegrant property was due to amylose fraction.

C. Rheological Studies of Pure Suspending Agents

1. Viscosity Determination of Pure Suspending Agents

Average apparent viscosities of each suspending agent at three different concentrations are presented in Table 9 and Figure 26. In all three concentrations, the viscosity of xanthan gum was determined by a SV1 sensor, which is used for a high

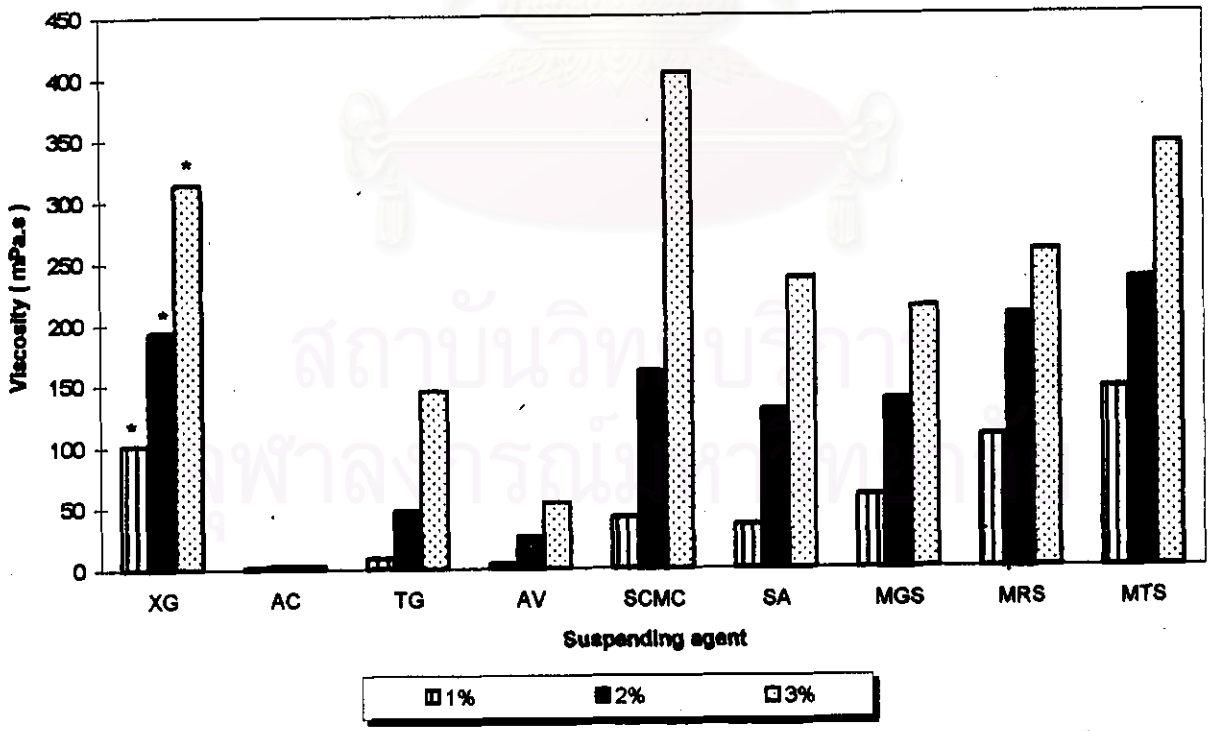
Table 9 Viscosity of Pure Suspending Agents at Varied Concentration

	Average Apparent Viscosity (mPas ± SD)								
	XG*	AC	TG	AV	SCMC	SA	MGS	MRS	MTS
1%	101.712 (57.448)	1.542 (0.734)	8.569 (0.585)	3.892 (1.579)	42.021 (6.923)	35.659 (3.869)	68.826 (22.201)	107.646 (42.400)	145.356 (67.849)
2%	193.230 (114.29)	2.851 (0.816)	47.664 (11.540)	26.929 (16.672)	160.450 (51.783)	128.619 (37.477)	136.861 (49.814)	205.510 (86.174)	234.344 (103.036)
3%	313.846 (202.815)	2.786 (0.552)	145.008 (57.723)	54.189 (35.028)	403.571 (161.794)	336.005 (122.546)	212.399 (81.030)	257.585 (107.182)	343.520 (149.351)

* determined by a different sensor (SV1)

XG = Xanthan Gum
AC = Acacia
TG = Tragacanth
MGS = Modified Glutinous Rice Starch
MRS = Modified Rice Starch
AV = Avicel RC-591
SCMC = Sod.Carboxymethylcellulose
SA = Sod.Alginate
MTS = Modifed Tapioca Starch

Figure 26 Viscosity of Pure Suspending Agents at Varied Concentration



viscous agent, and therefore the values were not compared to others. It is considered as the most viscous agent among all suspending agents evaluated in this study. Without xanthan gum, the order of decreasing viscosities are as follow; at 1% concentration - MTS > MRS > MGS > SCMC > SA > TG > AV > AC, at 2% concentration - MTS > MRS > SCMC > MGS > SA > TG > AV > AC, at 3% concentration - SCMC > MTS > MRS > SA > MGS > TG > AV > AC. Among different concentrations, the viscosity of each suspending agent increased when the concentration was increased.

The results clearly indicated that MGS, MRS, and MTS possessed higher viscosity than AC, TG, and AV regardless the concentration used in the formulation. At 1 and 2% concentration, the viscosity of modified starches was also higher than SCMC and SA except that of 2% MGS (136.861 mPas) which is lower than the viscosity of 2% SCMC (160.450 mPas). At 3% concentration, SCMC (403.571 mPas) showed the highest viscosity while the viscosity of MTS (343.520 mPas) was comparable to that of SA (336.005 mPas). MGS and MRS possessed lower viscosity than SCMC and SA at 3% concentration.

2. Rheological Behaviors and Measurement of Thixotropy of Pure Suspending Agents

Flow curves of each pure modified starch are shown in Figures 27-29. Those of other standard suspending agents are shown in Figures 30-32. All curves exhibited pseudoplastic flow characteristic with thixotropy. Thixotropic quantities, measured as a quantity of thixotropic breakdown, of pure suspending agents are determined and the comparative values are shown in Table 10 and Figure 33. The rheological behavior of

Figure 27 Flow Curves of Pure Modified Rice Starch at Concentration 1,2, and 3% w/v

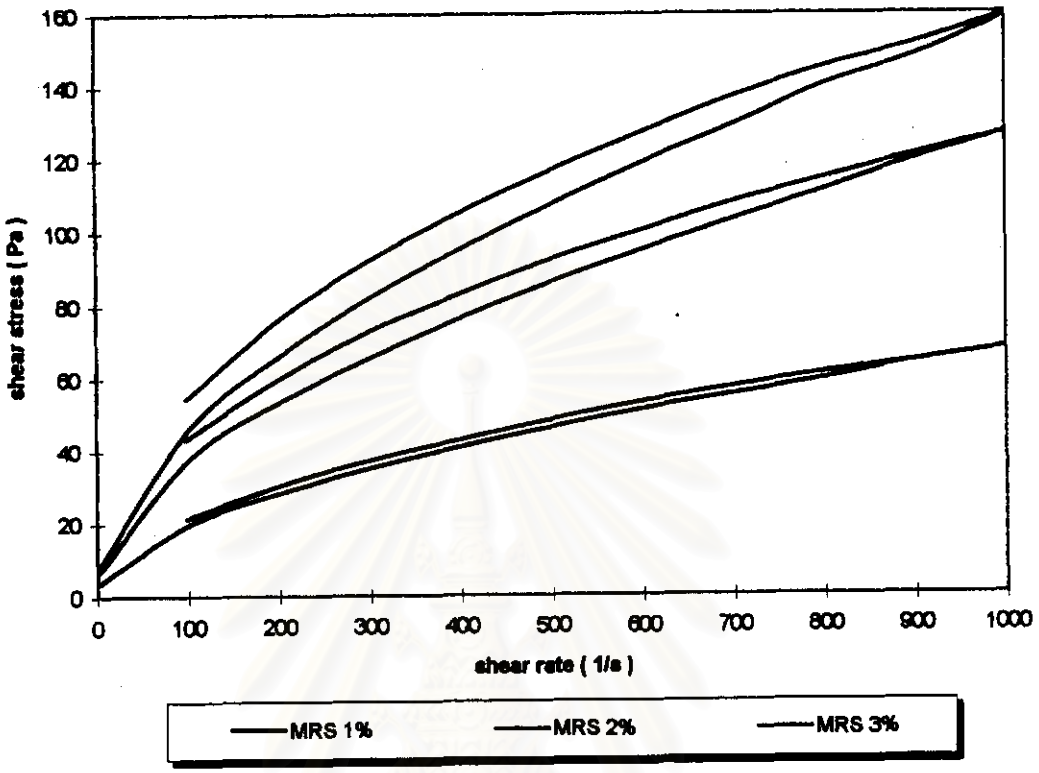


Figure 28 Flow Curves of Pure Modified Tapioca Starch at Concentration 1,2, and 3% w/v

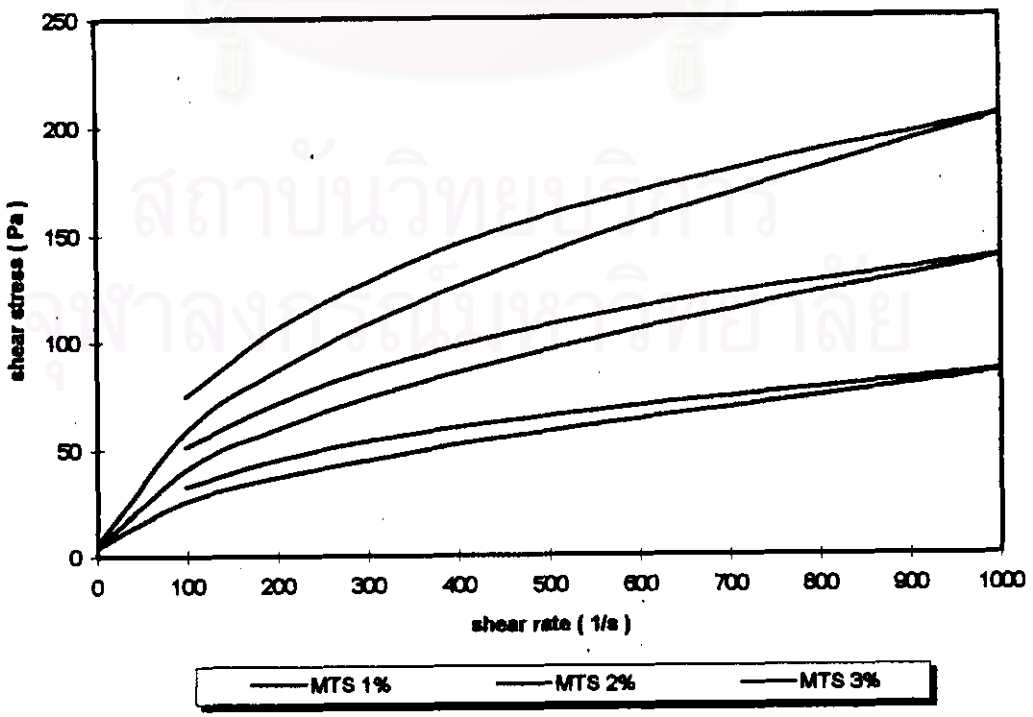


Figure 29 Flow Curves of Pure Modified Glutinous Rice Starch at Concentration 1,2, and 3% w/v

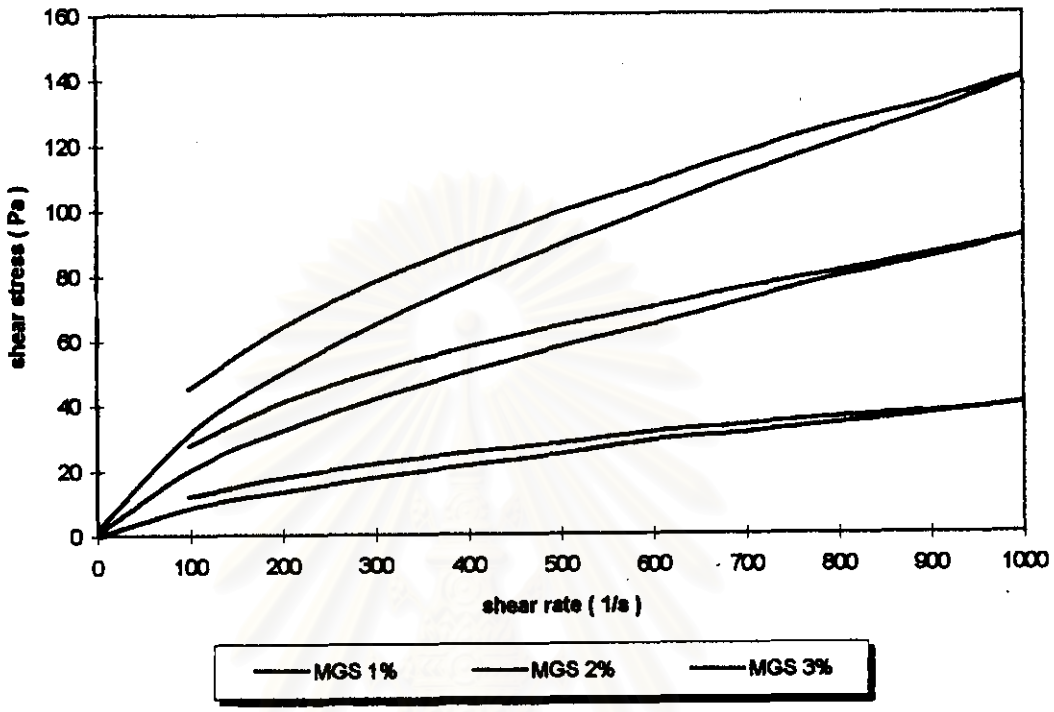


Figure 30 Comparative Flow Curves of Pure Suspending Agents at Concentration 1% w/v

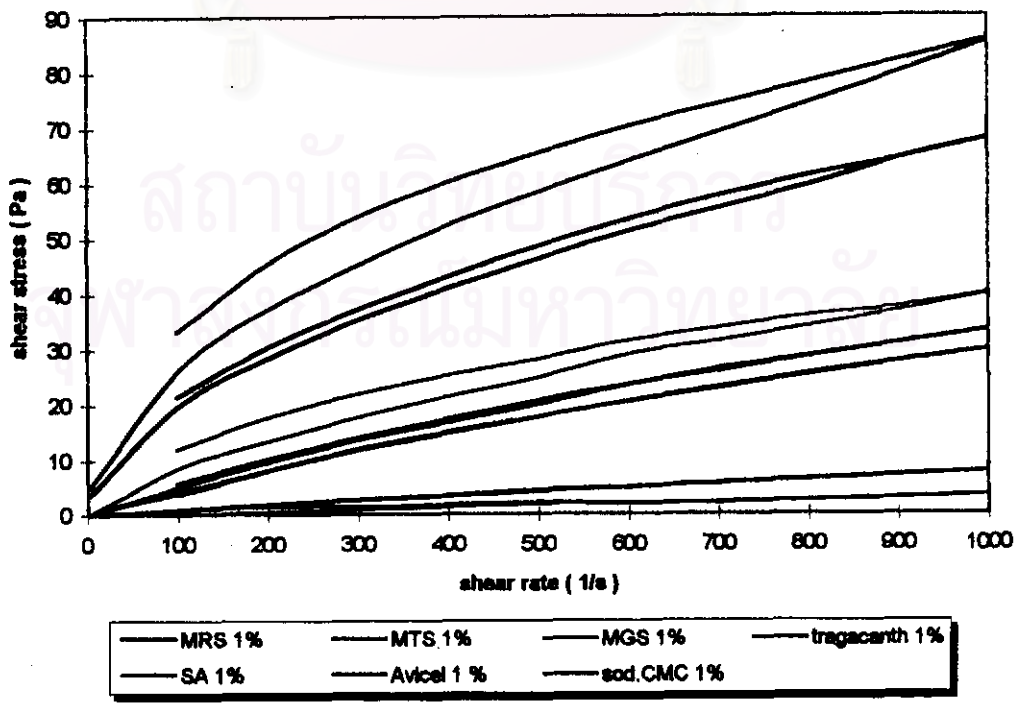


Figure 31 Comparative Flow Curves of Pure Suspending Agents at Concentration 2%w/v

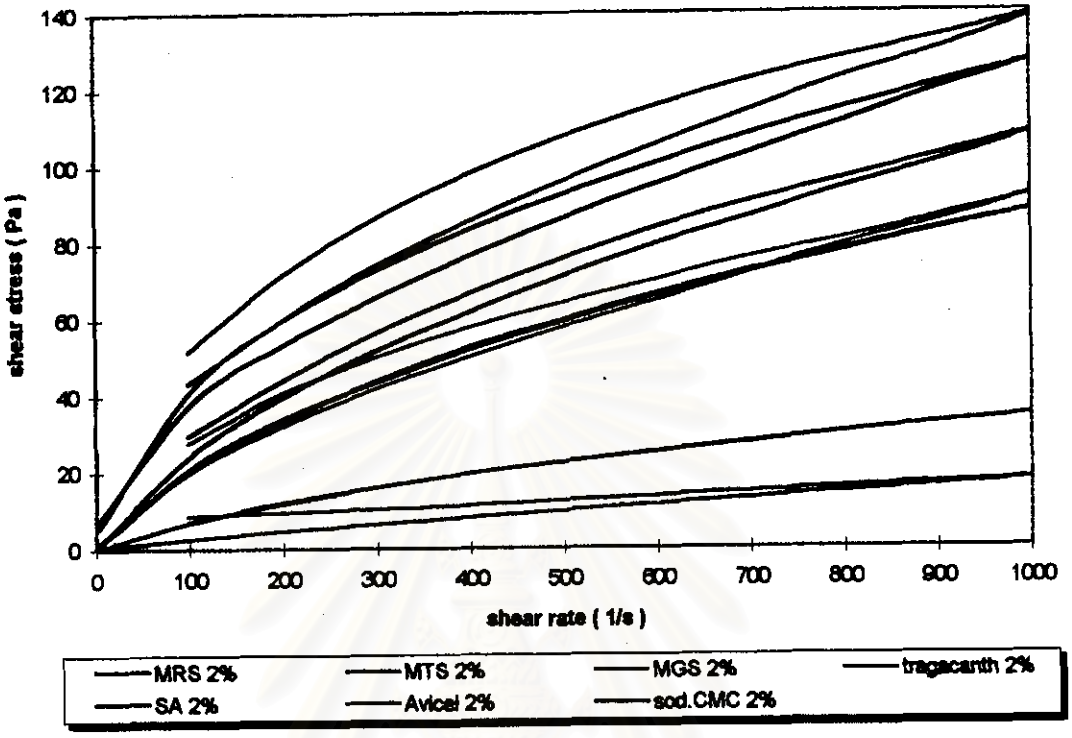


Figure 32 Comparative Flow Curves of Pure Suspending Agents at Concentration 3% w/v

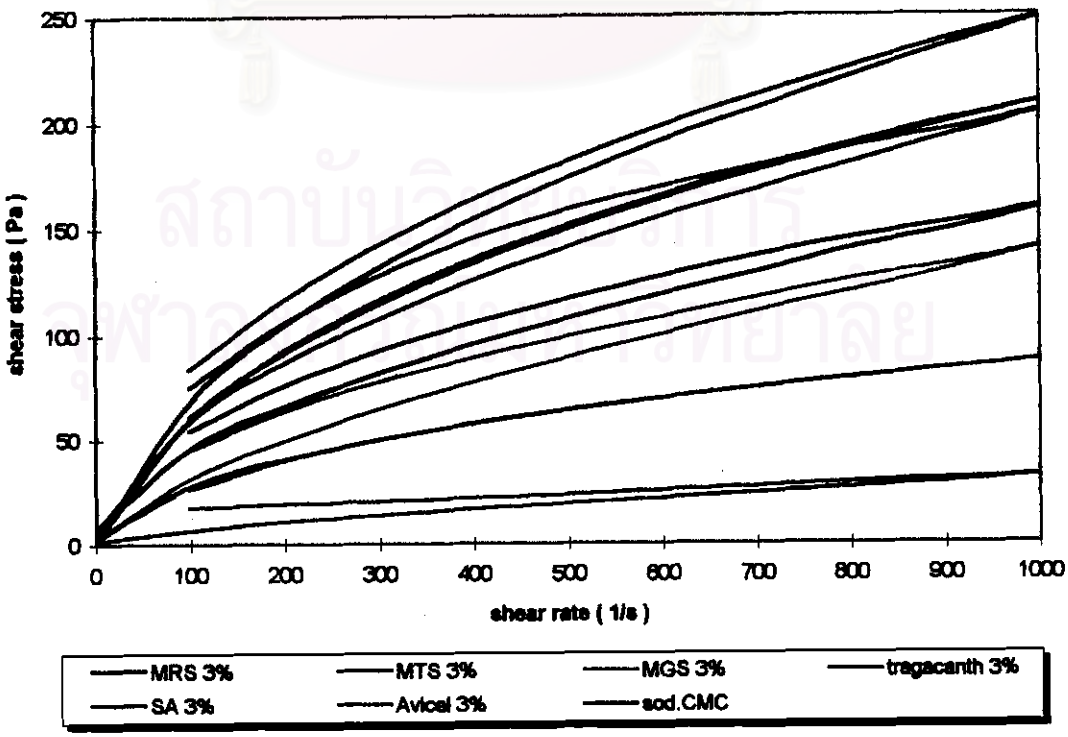
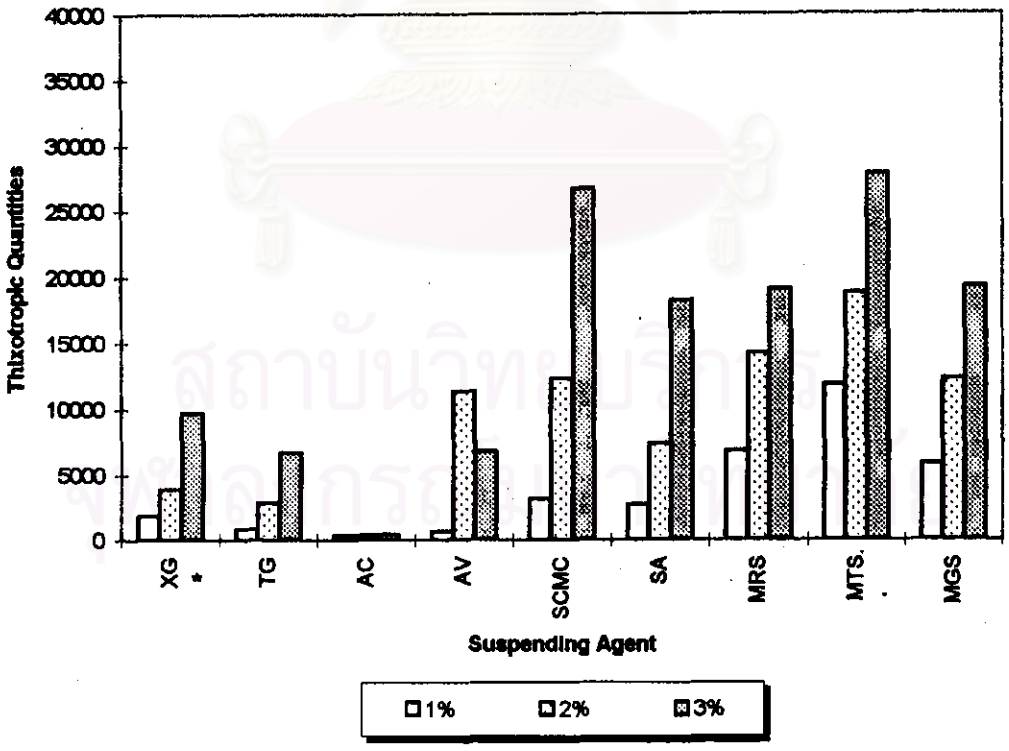


Table 10 Comparative Thixotropic Quantities of Pure Suspending Agents

Suspending Agent	1%	2%	3%
XG	1864	3918	9712
TG	842	2860	6700
AC	359	355	417
AV	663	11317	6770
SCMC	3130	12300	26700
SA	2690	7360	18200
MRS	6790	14160	19030
MTS	11810	18740	27800
MGS	5790	12230	19230

Figure 33 Comparative Thixotropic Quantities of Pure Suspending Agents



* used a different sensor (SV1)

XG was studied by a different sensor from the others and therefore was not compared in this measurement. The thixotropic quantity can be ranked in the following orders; at 1% concentration, MTS > MRS > MGS > SCMC > SA > TG > AV > AC, for 2% concentration, MTS > MRS > SCMC > MGS > AV > SA > TG > AC, and for 3% concentration, MTS > SCMC > MGS > MRS > SA > AV > TG > AC. The results explicited that MTS, at any concentration used, possessed the highest thixotropic quantity among all suspending agents employed in this study. The other two modified starches, MGS and MRS, also showed high thixotropic quantity comparable to that of SCMC and SA. At any concentration used in the study, thixotropic quantity of modified starches were much higher than that of TG, AC, and AV. Thixotropic quantity increased in accordance with increasing concentration in all cases except that of AV in which thixotropic quantity of 3% AV was lower than that of 2% AV. Thixotropy is a desirable characteristic in liquid pharmaceutical systems, including suspension. The high value of thixotropy, compared to other available suspending agents, obtained from modified starches suggested an application of these modified starches as suspending agent (Schramm, 1981).

D. Evaluation of Suspending Properties of Modified Starches Compared with Commercial Suspending Agents

1. Preparation of Ibuprofen Suspension

Twenty-seven ibuprofen suspensions (2 g/100 mL) containing nine different types and three different concentrations of suspending agents were successfully prepared. Most suspensions showed good stability and homogeneity after being

prepared except three suspensions those that contained MGS in which the contents were rapidly precipitated. An incompatibility between MGS and Tween^{R} 80 was suggested. After allowing the suspensions to stand for two weeks, ten more suspensions showed settlement of contents indicating that their suspending agents were unable to support the contents. All suspensions were subjected to SV determination, redispersibility, and rheology evaluations. Only those 14 suspensions in which the precipitation was not observed were tested for content uniformity. No major contamination was observed in all prepared suspensions over the evaluating period.

2. Evaluation of the Prepared Suspensions

Evaluation of modified starches as suspending agent was performed on ibuprofen suspension containing each modified starch. The evaluation was performed on four properties including SV determination, redispersibility, rheology, and content uniformity. The first three properties were evaluated under two conditions, normal 12 weeks and freeze-thaw (FT) cycle. Content uniformity was performed only under normal condition for 12 weeks. The results from these evaluations were compared to those obtained from other six commercial suspending agents: XG, SCMC, AC, AV, TG, and SA.

2.1 Sedimentation Volume Determination of Ibuprofen Suspensions

Sedimentation volume determination indicated the colloid-supporting or flocculating property of suspending agent. In suspension formulation, it is desirable to produce a partially flocculated dispersion in order to prevent caking and permit easy

redispersion (Martin, 1961). This property goes hand-in-hand with the viscosity i.e., the higher the viscosity, the better the sedimentation volume.

2.1.1 Normal Condition

SV of ibuprofen suspensions containing different concentrations of suspending agent were recorded at suitable time interval over a period of 12 weeks at room temperature. The results of SV of ibuprofen suspensions containing 1%, 2%, and 3% suspending agents are displayed in Figures 34, 35, and 36, respectively. At 1% concentration of suspending agents (Figure 34), suspensions that contained XG, MTS, and MRS possessed good SV with the final value of more than 0.90. SV of SCMC-containing suspension gradually decreased from 1.00 to 0.50 in 55 days and was steady afterward. SV of AV rapidly decreased to 0.55 in the first day but then remained steady through the evaluation period. Similar pattern was observed from suspension that contained TG with the final SV of 0.30. SV of suspensions that contained AC, SA, and MGS rapidly dropped to less than 0.10 within the first two days and remained steady afterward. The rank of decreasing SV is XG > MTS > MRS > SCMC > AV > TG > SA = MGS = AC.

At 2% concentration (Figure 35), SV of XG, MTS, and MRS-containing suspensions was 1.00 throughout the evaluation period. SV of suspension that contained SCMC dropped to 0.95 within 12 days and remained steady afterward. SV of suspensions that contained TG and AV was above 0.70. Suspensions that contained SA, MGS, and AC were precipitated, resulting in low SV from the start. Final SV of

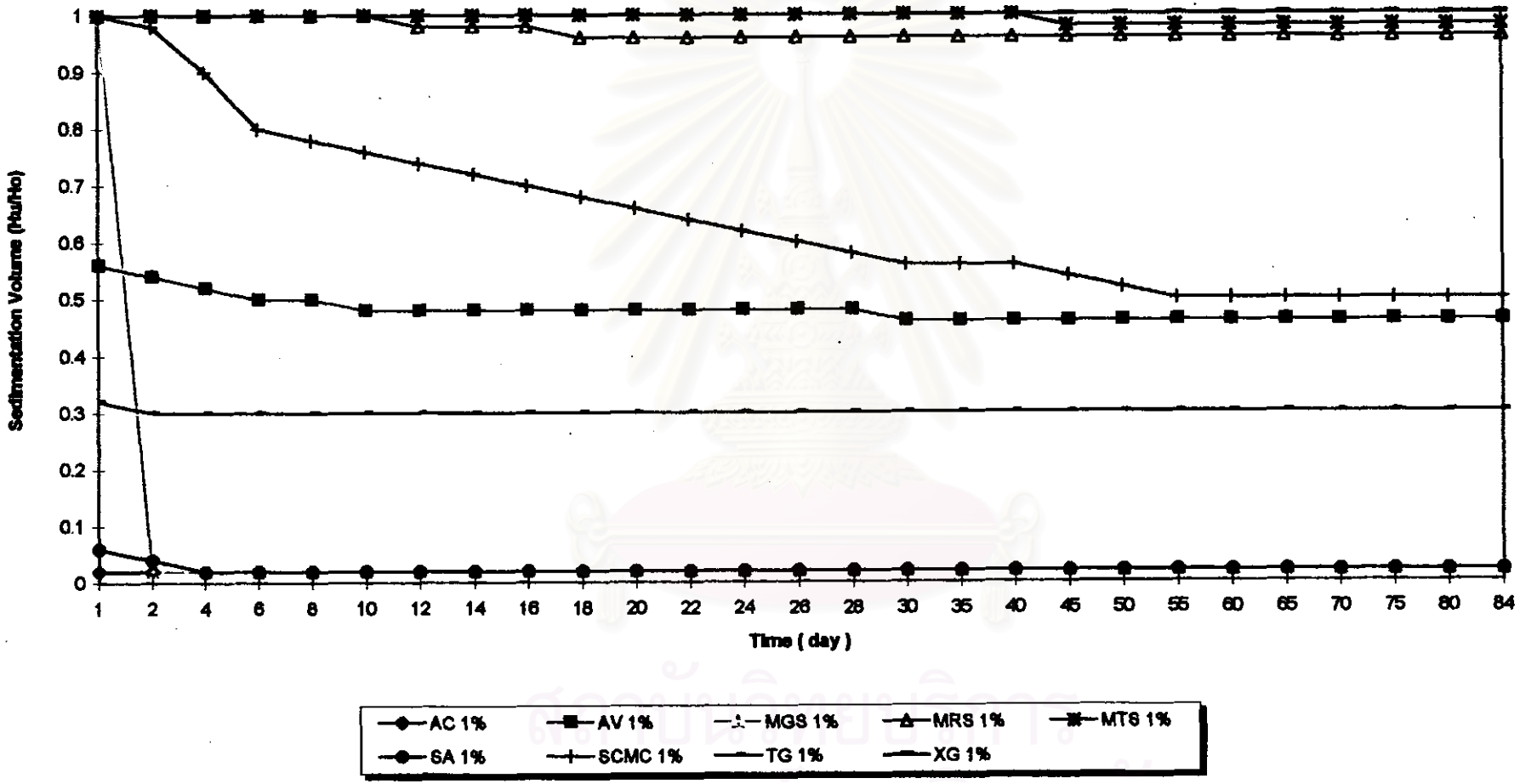


Figure 34 Sedimentation Volume of Ibuprofen Suspension Prepared Using 1% Suspending Agents - After 12 weeks

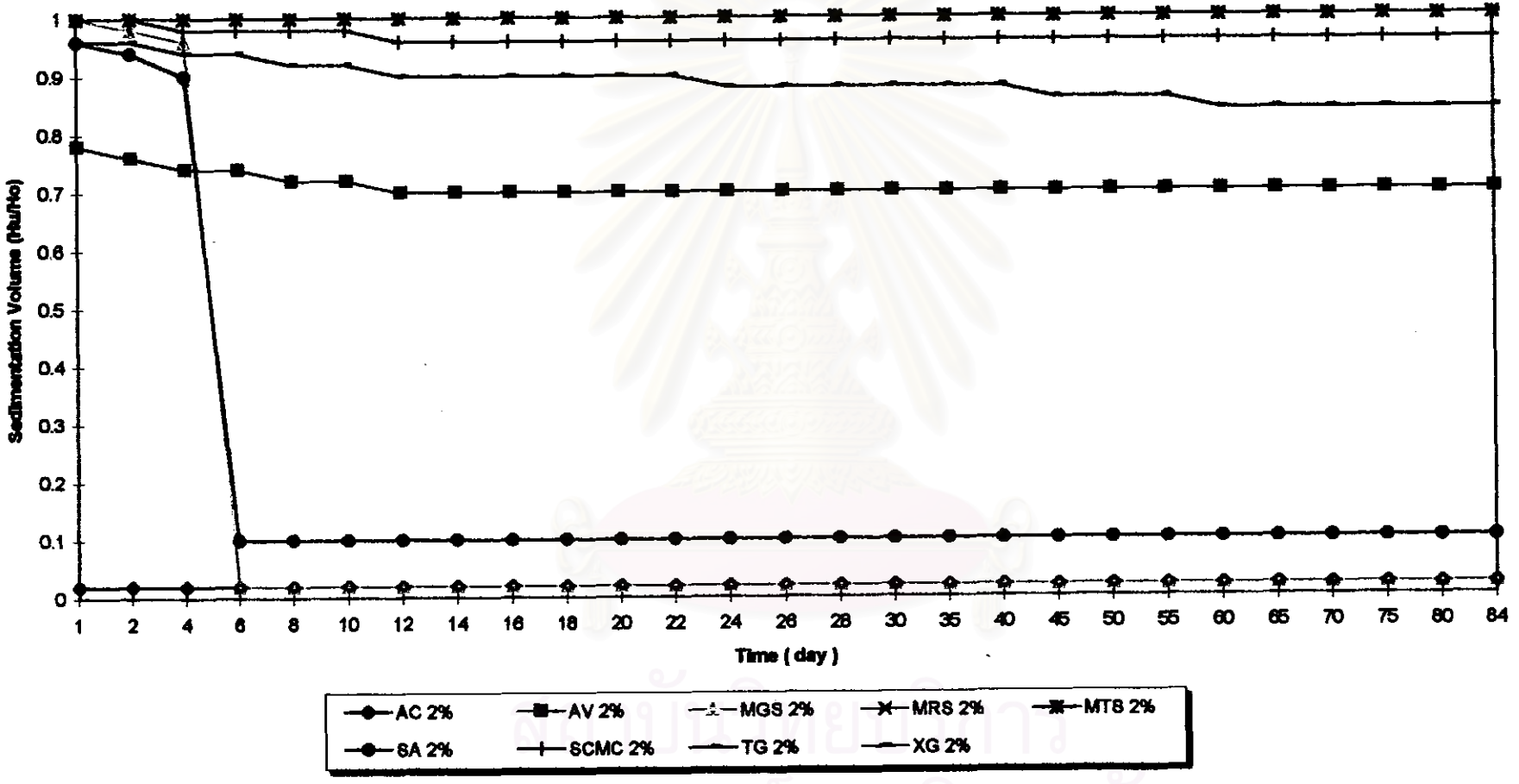


Figure 35 Sedimentation Volume of Ibuprofen Suspension Prepared Using 2% Suspending Agents - After 12 weeks

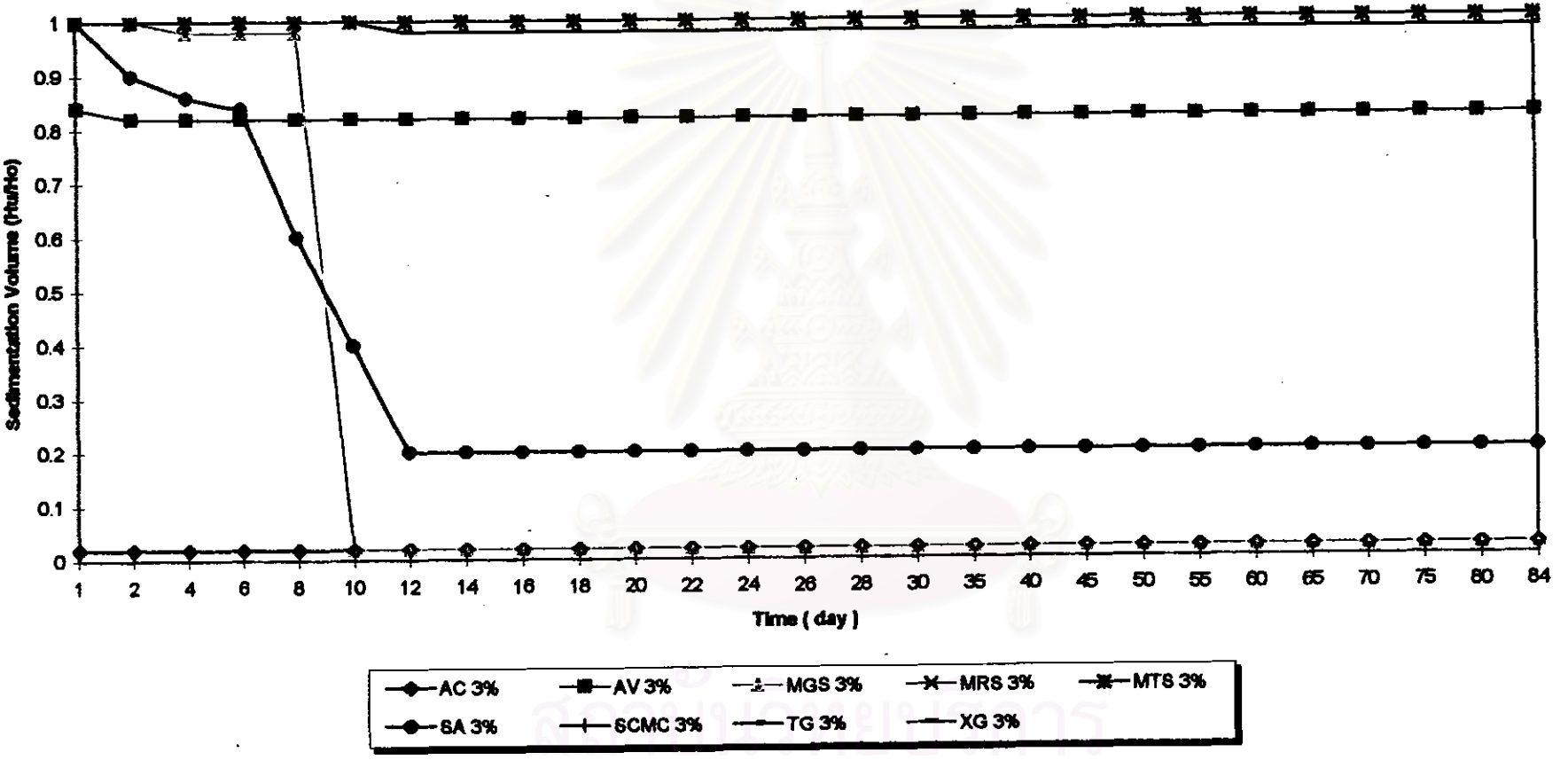


Figure 36 Sedimentation Volume of Ibuprofen Suspension Prepared Using 3% Suspending Agents - After 12 weeks

these suspensions was lower than 0.10. The rank of decreasing SV is XG = MTS = MRS > SCMC > TG > AV > SA > MGS = AC.

At 3% concentration (Figure 36), suspensions that contained XG, MTS, MRS, and SCMC showed good SV with the value of 1.00 throughout the evaluation period. SV of suspensions that contained TG and AV was steadily above 0.80. SV of MGS-containing suspension drop dramatically from 0.95 to 0.06 on day 10 and the value remained steady afterward. For SA-containing suspension, SV decreased from 1.00 to 0.20 within 12 days after being prepared and remained steady afterward. SV of AC-containing suspension was 0.02 from the first day due to precipitation of content. The rank of decreasing SV is XG = MTS = MRS = SCMC > TG > AV > SA > MGS = AC.

The final SV of ibuprofen suspensions containing different suspending agents evaluated after 12 weeks was shown in Table 11 and Figure 37. The results showed the increase in SV when the concentration of suspending agent was increased except for those contained AC and MGS in which SV were the same in all concentrations. The comparative appearance of SV of suspensions containing 1%, 2%, and 3% of each suspending agents evaluated after 12 weeks are shown in Figures 38-40. Considering the results obtained from all three concentrations, the overall rank of decreasing SV is XG > MTS > MRS > SCMC > TG > AV > SA > AC > MGS. The statistical analysis are presented in Tables 47-48 (Appendix II). It indicated that, in normal 12 weeks condition, no significant differences in final SV was observed among ibuprofen

Table 11 Sedimentation Volume of Ibuprofen Suspension Containing Different Suspending Agents - Final 12 weeks

Suspending Agent	1%	2%	3%
XG	1.00	1.00	1.00
SCMC	0.50	0.96	1.00
AV	0.46	0.70	0.82
TG	0.30	0.84	0.98
AC	0.02	0.02	0.02
SA	0.02	0.10	0.20
MTS	0.98	1.00	1.00
MRS	0.96	1.00	1.00
MGS	0.02	0.02	0.02

Figure 37 Sedimentation Volume of Ibuprofen Suspensions Containing Different Suspending Agents - Final 12 weeks

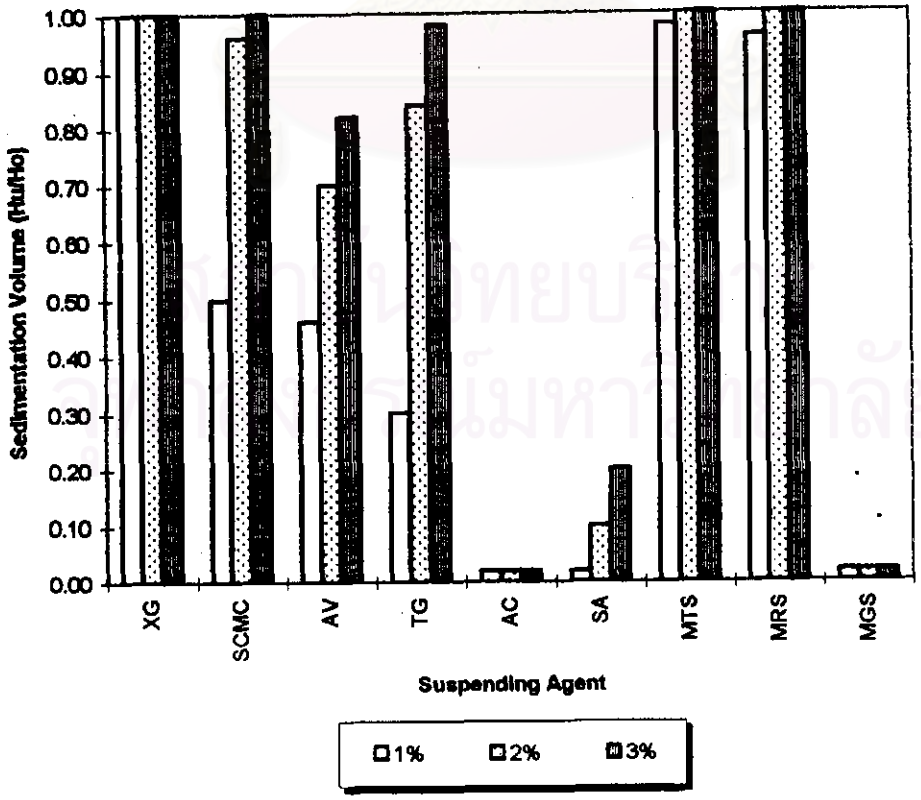


Figure 38 Final Sedimentation Volume of Ibuprofen Suspensions Containing 1% Suspending Agents - After 12 weeks at Room Temperature

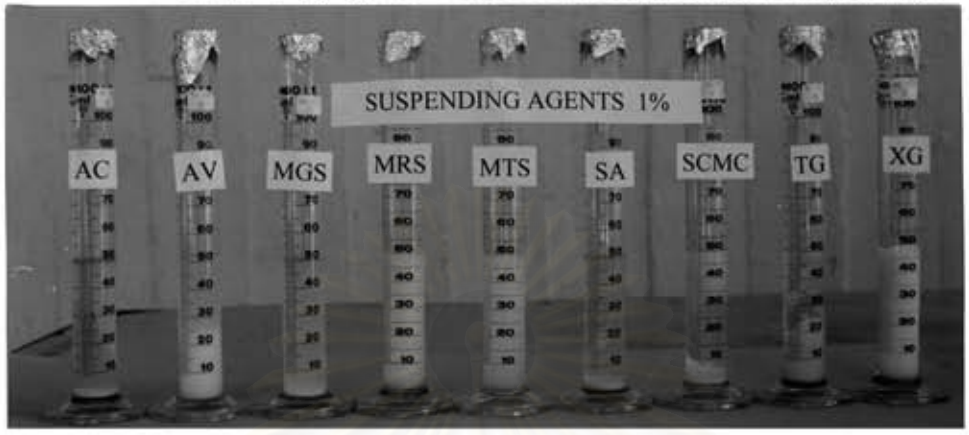


Figure 39 Final Sedimentation Volume of Ibuprofen Suspensions Containing 2% Suspending Agents - After 12 weeks at Room Temperature

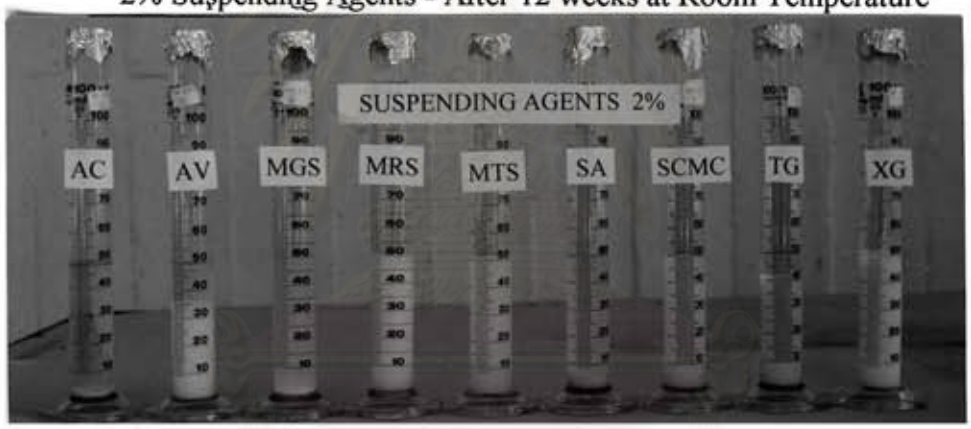
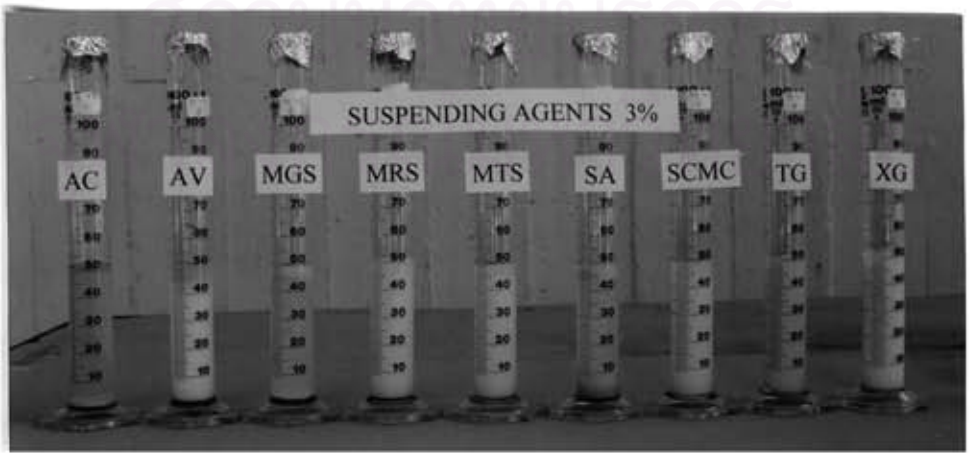


Figure 40 Final Sedimentation Volume of Ibuprofen Suspensions Containing 3% Suspending Agents - After 12 weeks at Room Temperature



suspensions that contained XG, MRS, MTS, or SCMC as suspending agent. The SV of suspension containing MGS, on the other hand, was significantly different from the others except that of SA and AC.

2.1.2 Freeze-Thaw Condition

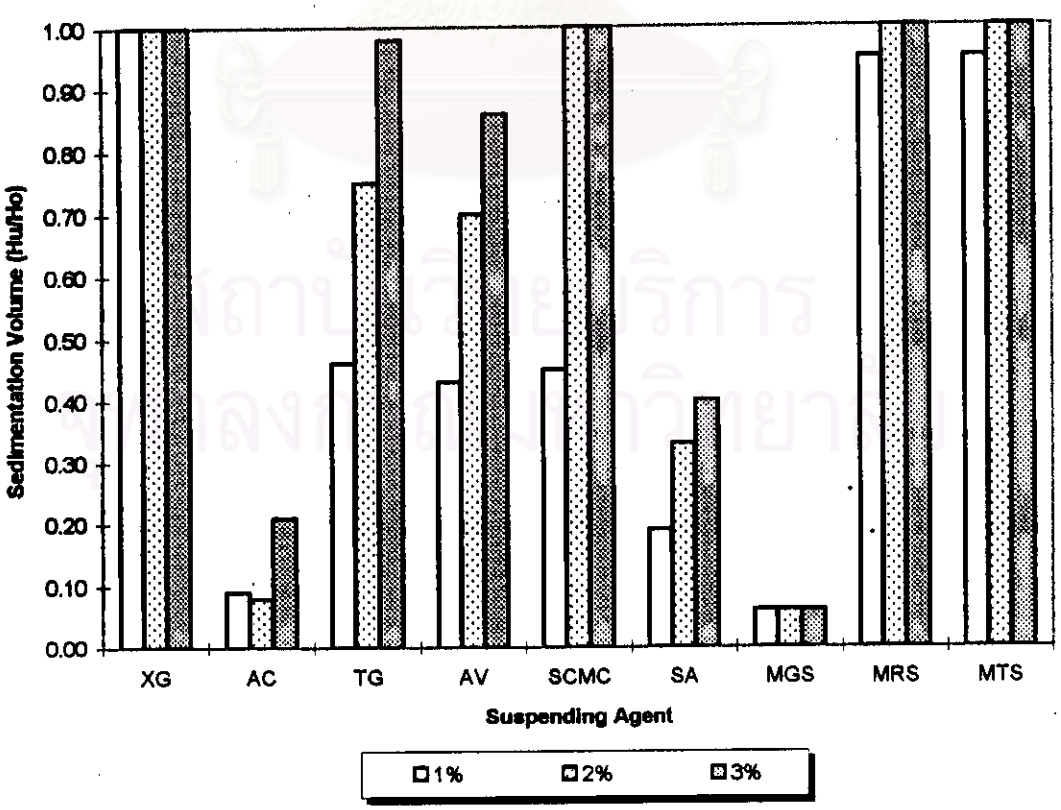
The final SV of ibuprofen suspensions containing different concentrations of suspending agent were recorded after the suspensions were treated under freeze-thaw condition. The results are shown in Table 12 and Figure 41. They can be ranked in the following orders; at 1% concentration, XG > MTS = MRS > TG > SCMC > AV > SA > AC > MGS, at 2% concentration, XG = MRS = MTS = SCMC > TG > AV > SA > AC > MGS, at 3% concentration, XG = MRS = MTS = SCMC > TG > AV > SA > AC > MGS.

The results showed the increase in SV when the concentration of suspending agent was increased except for those contained AC and MGS in which SV were similar in all concentrations. Considering the results obtained from all three concentrations, the overall rank of decreasing SV is XG > MTS = MRS > SCMC > TG > AV > SA > AC > MGS. The statistical analysis are presented in Tables 49-50 (Appendix II). It indicated that, under FT condition, no significant differences in final SV were observed among ibuprofen suspensions containing XG, MRS, MTS, or SCMC as suspending agent. The sedimentation volume of suspension containing MGS, on the other hand, was significantly different from the others except that of AC.

Table 12 Sedimentation Volume of Ibuprofen Suspension Containing Different Suspending Agents - Freeze-Thaw Condition

Suspending Agent	1%	2%	3%
XG	1.00	1.00	1.00
AC	0.09	0.08	0.21
TG	0.46	0.75	0.98
AV	0.43	0.70	0.86
SCMC	0.45	1.00	1.00
SA	0.19	0.33	0.40
MGS	0.06	0.06	0.06
MRS	0.95	1.00	1.00
MTS	0.95	1.00	1.00

Figure 41 Sedimentation Volume of Ibuprofen Suspensions Containing Different Suspending Agents - Freeze-Thaw Cycle



The comparative results of sedimentation volume tests under normal and FT conditions are shown in Tables 13-15 and Figures 42-44. In all suspending agents, the results showed no significant difference between the values obtained from both conditions. The results from the evaluations under both conditions explicited that, from the SV point of view, MRS and MTS were as promising suspending agent as XG and SCMC and were clearly better than TG, AV, SA, and AC, regardless the concentration used in the study. In case of MGS-containing suspension, an incompatibility has occurred and resulted in low sedimentation volume in all three concentration (SV = 0.02 and 0.06 in normal and FT condition, respectively). Additional experiment, by mixing MGS with each of formulation ingredients, revealed that there was an incompatibility between MGS and Tween^{R} 80, a surfactant used in suspension formulation. The mechanism of this interaction, which caused a viscosity loss in MGS, was unknown. As a result, the sedimentation volume of suspensions that contained MGS were as poor as those that contained SA and AC.

2.2 Redispersibility of Ibuprofen Suspensions

Redispersibility is another required characteristic of well-formulated suspension. It indicated the ability of suspending agent in preventing a packing or caking of colloids. Practically, redispersibility evaluation was performed by recording the number of inversion required to resuspend the pre-settled suspension. The less number of inversion used, the better the redispersibility (Lieberman, Rieger, and Banker, 1988).

Table 13 Comparative Sedimentation Volume of Ibuprofen Suspension Containing 1% of Different Suspending Agents - FT v.s After 12 weeks

Suspending Agent	1%	
	Normal	FT
XG	1.00	1.00
AC	0.02	0.09
TG	0.30	0.46
AV	0.46	0.43
SCMC	0.50	0.45
SA	0.02	0.19
MGS	0.02	0.06
MRS	0.96	0.95
MTS	0.98	0.95

Figure 42 Comparative Final Sedimentation Volume of Ibuprofen Suspensions Containing 1% Suspending Agents - 2 Conditions

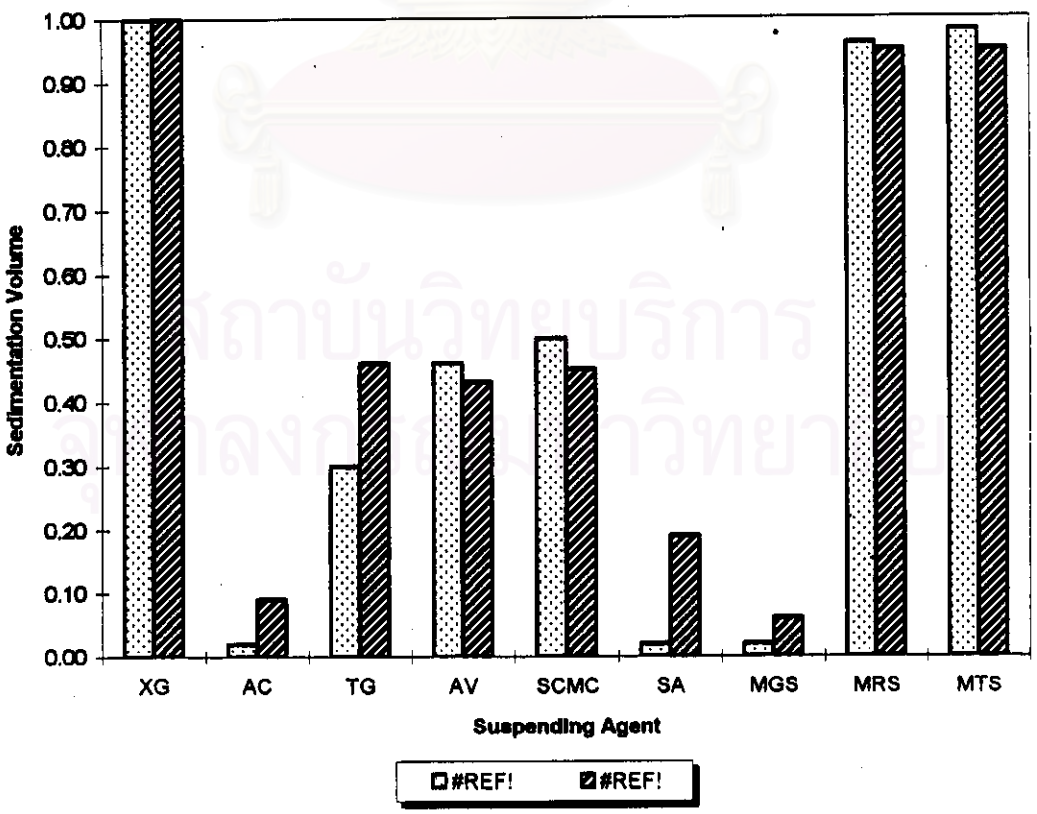


Table 14 Comparative Sedimentation Volume of Ibuprofen Suspension Containing 2% of Different Suspending Agents - FT v.s After 12 weeks

Suspending Agent	2%	
	Normal	FT
XG	1.00	1.00
AC	0.02	0.08
TG	0.84	0.75
AV	0.70	0.70
SCMC	0.96	1.00
SA	0.10	0.33
MGS	0.02	0.06
MRS	1.00	1.00
MTS	1.00	1.00

Figure 43 Comparative Final Sedimentation Volume of Ibuprofen Suspensions Containing 2% Suspending Agents - 2 Conditions

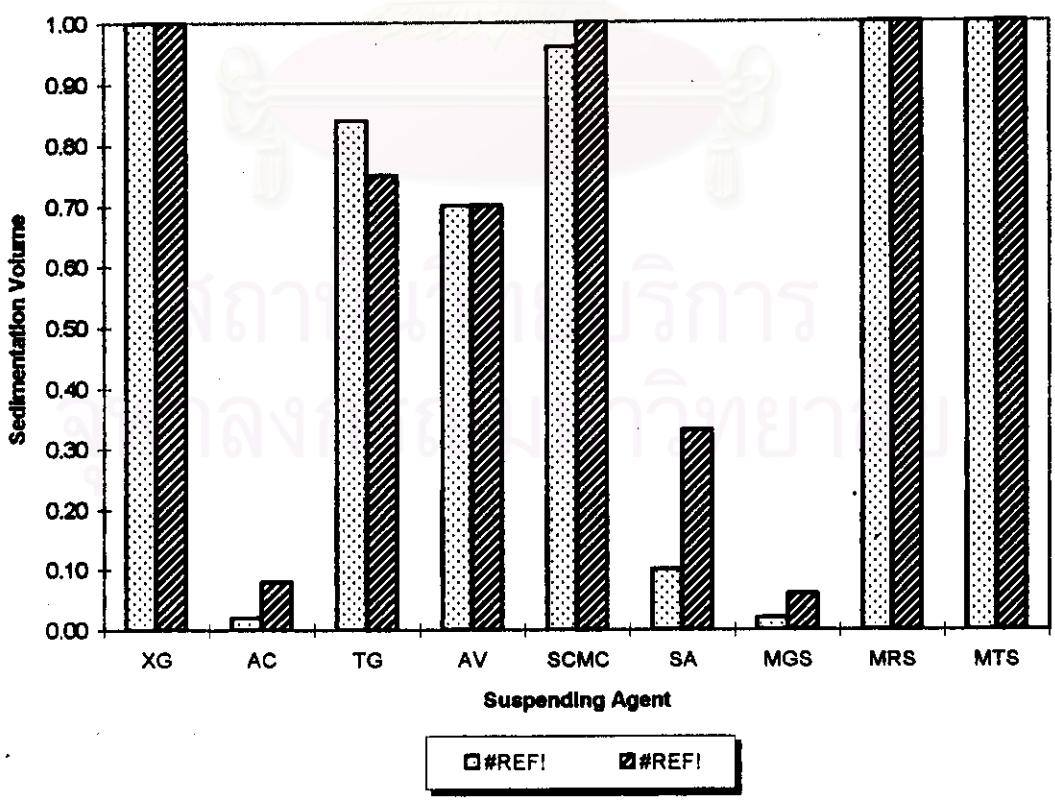
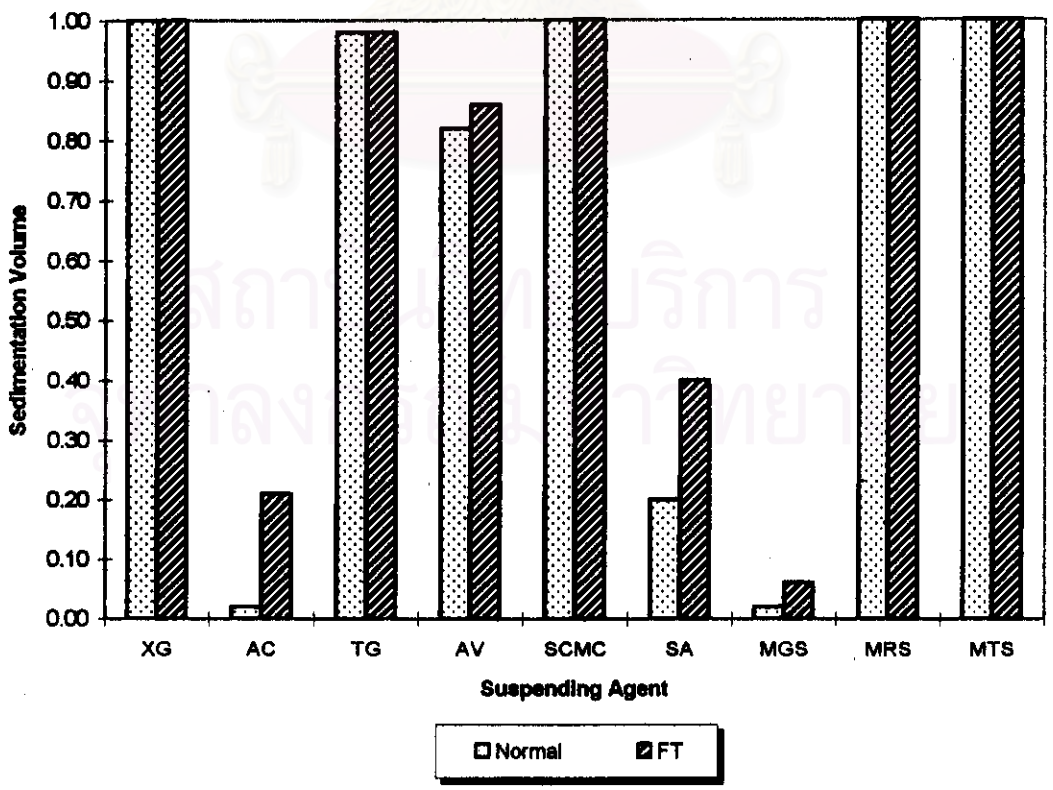


Table 15 Comparative Sedimentation Volume of Ibuprofen Suspension Containing 3% of Different Suspending Agents - FT v.s After 12 weeks

Suspending Agent	3%	
	Normal	FT
XG	1.00	1.00
AC	0.02	0.21
TG	0.98	0.98
AV	0.82	0.86
SCMC	1.00	1.00
SA	0.20	0.40
MGS	0.02	0.06
MRS	1.00	1.00
MTS	1.00	1.00

Figure 44 Comparative Final Sedimentation Volume of Ibuprofen Suspensions Containing 3% Suspending Agents - 2 Conditions



2.2.1 Normal Condition

The redispersibility of ibuprofen suspensions storing under normal condition was evaluated every two weeks and the results are shown in Table 16. Regardless the concentration used in the study, MRS and MTS appeared to provide good redispersible property to the suspension comparable to that of XG. Ibuprofen suspensions that contained these three suspending agents needed zero or only one inversion to regain dispersion, at all three concentrations. At 1% concentration, suspensions that contained SCMC required four inversions to redisperse. At 2% and 3% concentration, SCMC required zero or only one inversion for redispersion. Other suspending agents that also showed promising result on this property were 1 to 3% AC (4-5 inversions), 1 to 3% AV (1-2 inversions), and 2 to 3% TG (1-4 inversions). The redispersibility of suspensions that contained 1-2% MGS were acceptable for they regained redispersion within 12 inversions. Suspensions that did not exhibit good redispersible property were those containing 3% MGS, 1 to 3% SA and 1% TG. These suspensions required vigorous shaking to obtain redispersion.

Regarding the concentration used, redispersibility of suspension that contained SCMC, TG , AC, and AV improved when the concentration increased. These four suspending agents were viscous compounds that possessed the colloid-supporting ability. In contrast, redispersibility of suspensions that contained SA subsided when the concentration increased, indicating that SA was unable to support colloids. The number of inversion required for suspensions that contained MGS increased when the concentration increased.. In MTS, MRS, and XG cases, their redispersibility was not

Table 16 Numbers of Inversion Required to Redisperse Ibuprofen Suspensions Containing Different Suspending Agents - Normal Condition

Suspending Agent	%	Number(s) of Inversion					
		Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Acacia	1	4	5	5	5	5	5
	2	4	4	4	4	4	4
	3	4	4	4	4	4	4
Avicel RC-591	1	2	2	2	2	2	2
	2	2	2	2	2	2	2
	3	1	1	1	1	1	1
Sodium Alginate	1	11	vs	vs	vs	vs	vs
	2	vs	vs	vs	vs	vs	vs
	3	vs	vs	vs	vs	vs	vs
SCMC	1	3	4	4	4	4	4
	2	1	1	1	1	1	1
	3	0	0	0	0	0	0
Tragacanth	1	vs	vs	vs	vs	vs	vs
	2	4	4	4	4	4	4
	3	1	1	1	1	1	1
Xanthan Gum	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
MGS DS 0.16	1	12	12	12	12	12	12
	2	12	12	12	12	12	12
	3	12	12	vs	vs	vs	vs
MRS DS 0.26	1	1	1	1	1	1	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
MTS DS 0.39	1	0	0	0	1	1	1
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0

vs = vigorously shaken

affected by concentration since all of them required zero or only one inversion to redisperse.

2.2.2 Freeze-Thaw Condition

The redispersibility of ibuprofen suspensions storing under FT condition was evaluated at the end of the last cycle and the results are shown in Table 17. It is shown that, under this condition, suspensions that contained 1 to 3% MRS, 1 to 3% MTS, 1 to 3% XG, 1% TG, and 2 to 3% SCMC required zero or only one inversion to redisperse. These suspensions, therefore, possessed good redispersibility. Other suspending agents that showed promising redispersibility under this condition were 1% SCMC (4 inversions), 1% AV (3 inversions), 3% SA (4 inversions). Suspensions containing 2 to 3% AV, 2% TG, and 1 to 3% MGS showed somewhat acceptable results i.e.; required not more than 12 inversions. Suspensions that did not exhibit good redispersible property included those that contained 1 to 3% AC, 1 to 2% SA, and 1% TG for they required vigorous shaking to redisperse.

Under FT condition, the results showed that the redispersibility of suspensions that contained SCMC, TG ,and SA decreased when the concentration increased. In contrast, redispersibility of suspensions that contained AV increased when the concentration increased. The redispersibility of suspensions that contained AC, XG, MGS, MRS, and MTS was not affected by concentration.

Table 17 Numbers of Inversion Required to Redisperse Ibuprofen Suspensions Containing Different Suspending Agents - Freeze Thaw Condition

Suspending Agent	%	No. of Inversion
Acacia	1	vs
	2	vs
	3	vs
Avicel RC-591	1	3
	2	7
	3	9
Sodium Alginate	1	vs
	2	vs
	3	4
SCMC	1	4
	2	0
	3	0
Tragacanth	1	vs
	2	10
	3	1
Xanthan Gum	1	0
	2	0
	3	0
MGS DS 0.16	1	10
	2	10
	3	10
MRS DS 0.26	1	1
	2	0
	3	0
MTS DS 0.39	1	1
	2	0
	3	0

vs = vigorously shaken

The comparative evaluation of ibuprofen suspensions on final redispersibility under normal 12 weeks condition and FT condition is presented in Table 18. On one-by-one comparison, the redispersibility of suspensions that contained the same type and concentration of suspending agent obtained from different condition were comparable. The exception was noted in cases of 1 to 3% AC, 2 to 3% AV, and 3% SA. For AC, the number of inversion required to redisperse was four to five times under normal 12 weeks conditions compared to vigorous shaking under FT condition. For AV, the number of inversion required to redisperse was 2 and 1 for 2% and 3% concentration, respectively under normal 12 weeks condition compared to 7 and 9 times for 2% and 3%, respectively under FT condition. For 3% SA containing suspension, vigorous shaking was required under normal 12 weeks condition compared to 4 inversions required under FT condition. The results under both normal and FT conditions suggested that MRS and MTS are exceptional suspending agents for they required zero or only one inversion to redisperse under both normal 12 weeks and FT conditions. The redispersibilty of MRS and MTS containing suspensions were comparable to that of XG and SCMC, two commonly used suspending agents. The stability of suspension containing MRS and MTS under both normal 12 weeks and FT conditions was found superior than AC, which was stable only under normal 12 weeks condition. Although MGS has exhibited an outstanding redispersibility when employed in calcium carbonate suspension (Table 4), it was not considered a good suspending agent in this study for it lost the redispersibility when employed in ibuprofen suspension under both conditions.

Table 18 Comparison of Numbers of Inversion Required to Redisperse Ibuprofen Suspension Containing Different Suspending Agents

Suspending Agent	%	Number(s) of Inversion	
		Normal	Freeze-Thaw
Acacia	1	5	vs
	2	4	vs
	3	4	vs
Avicel RC-591	1	2	3
	2	2	7
	3	1	9
Sodium Alginate	1	vs	vs
	2	vs	vs
	3	vs	4
SCMC	1	4	4
	2	1	0
	3	0	0
Tragacanth	1	vs	vs
	2	4	10
	3	1	1
Xanthan Gum	1	0	0
	2	0	0
	3	0	0
MGS DS 0.16	1	12	10
	2	12	10
	3	vs	10
MRS DS 0.26	1	1	1
	2	0	0
	3	0	0
MTS DS 0.39	1	1	1
	2	0	0
	3	0	0

vs = vigorously shaken

2.3 Rheological Study of Ibuprofen Suspensions

2.3.1 Viscosity Determination of Ibuprofen Suspensions

The average apparent viscosities of modified starch-containing ibuprofen suspensions evaluated under initial, normal 12 weeks, and FT conditions are presented in Tables 19-21. The results showed that, regardless the type of modified starch and concentration used in the study, the viscosity of suspension in initial condition was higher than that of suspension in normal 12 weeks condition, and also higher than that of suspension treated under freeze-thaw condition. This observation suggested that lost of vehicle structure has occurred when suspension was stored for a period of time.

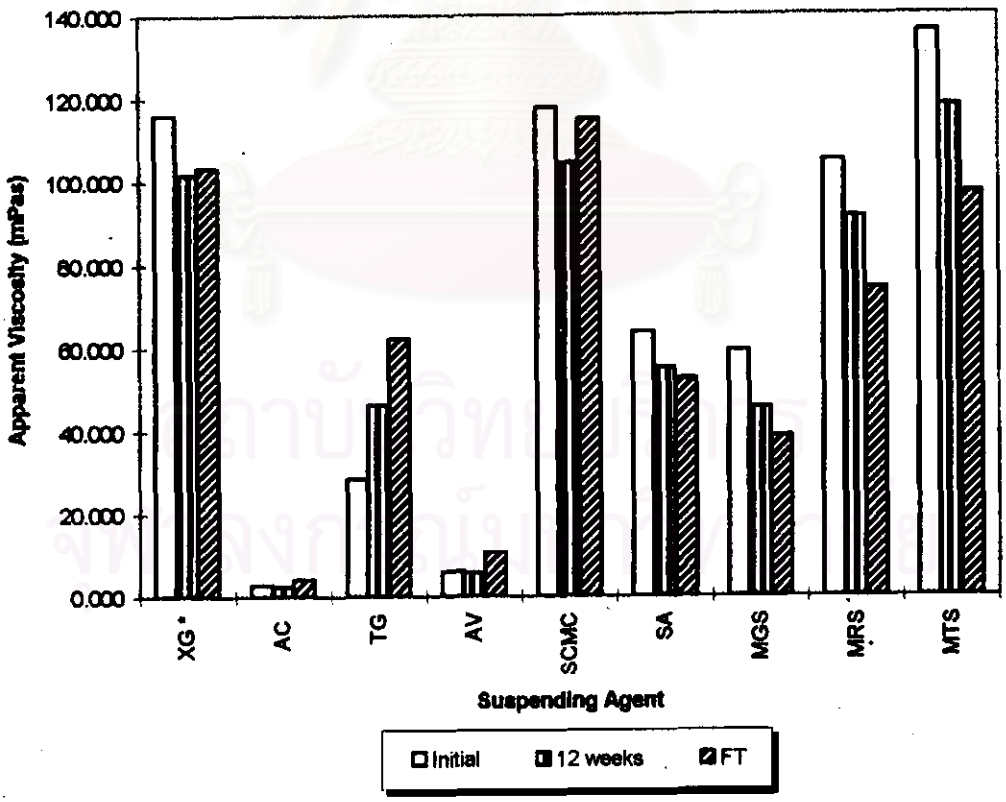
The comparative viscosities among suspensions containing 1, 2, and 3% suspending agents are shown in Figures 45, 46, and 47, respectively. At 1% concentration, suspensions that contained SA, MGS, MRS, and MTS showed similar order of viscosity among three conditions. In these suspensions, the viscosity of initial > normal 12 weeks > FT. The order of viscosities of suspension that contained XG and SCMC were initial > FT > normal 12 weeks. For AV and AC, the order was FT > initial > normal 12 weeks. For TG, the order of decreasing viscosity was FT > normal 12 weeks > initial.

At 2% concentration (Figure 46), the results were the same as those of 1% concentration except for XG in which the order of decreasing viscosity was normal 12 weeks > initial > FT.

Table 19 Viscosity of Ibuprofen Suspension Containing 1% Suspending Agent Evaluated in three Conditions

Suspending Agents	Viscosity (mPas)			Sensor Used
	Initial	12 weeks	FT	
XG *	116.015	101.646	103.303	SV1
AC	2.667	2.386	4.028	NV
TG	28.342	46.313	62.260	MV1
AV	6.000	5.724	10.567	NV
SCMC	117.729	104.278	114.831	MV1
SA	63.740	55.038	52.367	MV1
MGS	59.139	45.516	38.483	MV1
MRS	104.764	91.259	73.997	MV1
MTS	135.855	117.921	96.934	MV1

Figure 45 Viscosity of Ibuprofen Suspension Containing 1% Suspending Agent Evaluated in three Conditions

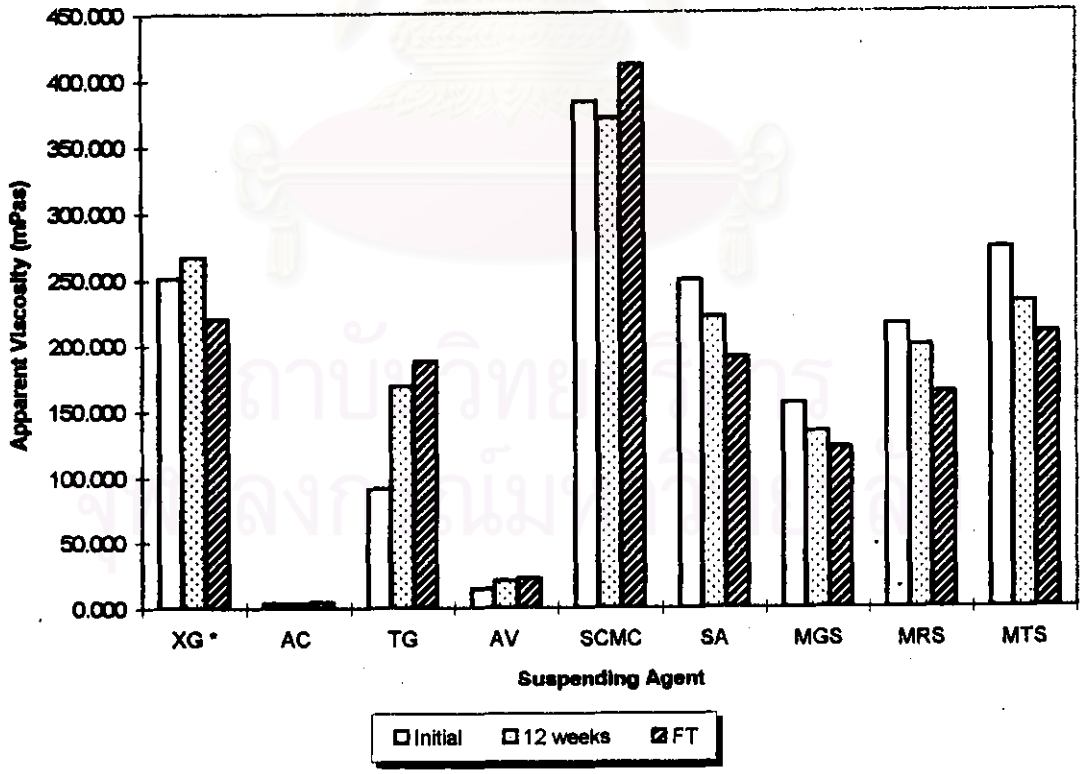


* used a different sensor (SV1)

Table 20 Viscosity of Ibuprofen Suspension Containing 2% Suspending Agent Evaluated in three Conditions

Suspending Agents	Viscosity (mPas)			Sensor Used
	Initial	12 weeks	FT	
XG *	250.927	266.748	219.865	SV1
AC	3.540	3.161	4.485	NV
TG	91.162	168.960	187.665	MV1
AV	14.289	20.645	22.402	NV
SCMC	382.828	370.349	410.024	MV1
SA	249.068	220.753	190.218	MV1
MGS	155.597	133.632	121.922	MV1
MRS	215.290	199.000	162.854	MV1
MTS	272.185	231.625	208.053	MV1

Figure 46 Viscosity of Ibuprofen Suspension Containing 2% Suspending Agent Evaluated in three Conditions

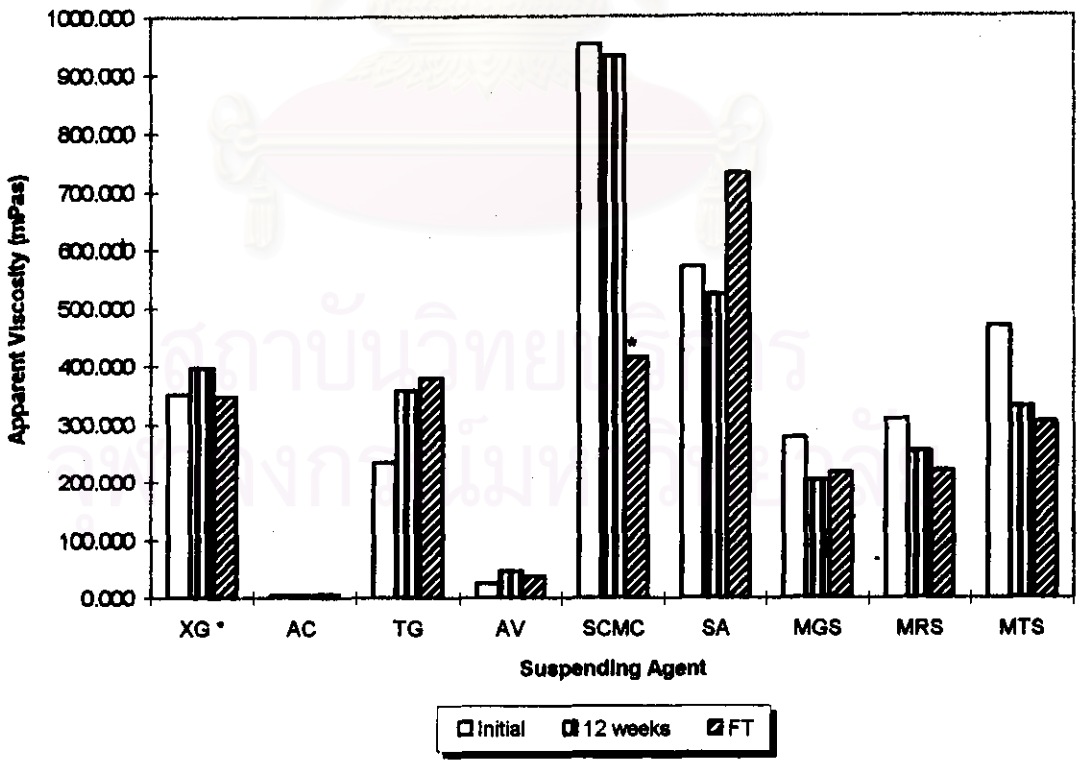


* used a different sensor (SV1)

Table 21 Viscosity of Ibuprofen Suspension Containing 3% Suspending Agent Evaluated in three Conditions

Suspending Agents	Viscosity (mPas)			Sensor Used
	Initial	12 weeks	FT	
XG *	350.738	396.986	346.492	SV1
AC	4.497	4.865	5.380	NV
TG	234.152	356.602	378.615	MV1
AV	24.571	46.486	37.395	NV
SCMC	951.315	931.457	415.167	MV1,SV1
SA	569.389	522.481	729.856	MV1
MGS	277.015	202.762	216.052	MV1
MRS	308.287	252.866	219.026	MV1
MTS	467.342	329.185	302.273	MV1

Figure 47 Viscosity of Ibuprofen Suspension Containing 3% Suspending Agent Evaluated in three Conditions



* used a different sensor (SV1)

At 3% concentration (Figure 47), the order of decreasing viscosity of suspensions that contained SCMC, MRS, and MTS was initial > normal 12 weeks > FT. For SA, the order of decreasing viscosity was FT > initial > normal 12 weeks. For AC and TG, the order of decreasing viscosity was FT > normal 12 weeks > initial. For AV, the viscosity of normal 12 weeks > FT > initial. And for XG, the order of decreasing viscosity was normal 12 weeks > initial > FT.

Suspensions that contained TG, MRS, and MTS as suspending agent were three groups of suspensions in which the viscosity pattern was consistent at all three concentrations. In MRS and MTS cases, the order of initial > normal 12 weeks > FT suggested that these two modified starches underwent regular degradating pattern in which degradation took place as time proceeded and occurred the most under stress condition (Zatz, 1985). Tragacanth was the only suspending agent that exhibited the order of FT > normal 12 weeks > initial. In normal 12 weeks condition, the increase in viscosity of TG-containing suspensions was due to either the loss of water or the fully swelling of the gum. Under FT condition, the fact that TG was subjected to temperature depletion explained the increase in viscosity at the end of the evaluation. Tragacanth swells in water to produce a highly viscous colloidal dispersion. In fact, the highest viscosities are obtained when solutions are made in cold water (Zatz, Berry, and Alderman, 1988).

Table 22 focuses on the comparative viscosity of ibuprofen suspensions that contained three concentrations of modified starches evaluated under three conditions.

The results from all three conditions shared the same changing patterns of viscosity that MTS possessed the highest viscosity among all three modified starches and that the viscosity of modified starches increased when the concentration increased. In addition, the order of decreasing viscosity among three conditions was initial > normal 12 weeks > FT in all suspension except the one that contained 3% MGS in which the order of viscosity was initial > FT > normal 12 weeks.

The comparative viscosity of ibuprofen suspensions containing varied concentrations of suspending agents evaluated in three conditions are shown in Figures 48-50. Regardless the conditions and types of suspending agent, the viscosity increased when the concentration increased. In initial condition (Figure 48), the viscosity of suspensions was ranked in the following orders; at 1% concentration, MTS > SCMC > MRS > SA > MGS > TG > AV > AC; at 2% concentration, SCMC > MTS > SA > MRS > MGS > TG > AV > AC; at 3% concentration, SCMC > SA > MTS > MRS > MGS > TG > AV > AC.

Figure 49 illustrates the viscosity of suspensions evaluated after 12 weeks of storing. The viscosity of suspensions from this condition was ranked in the following orders; at 1% concentration, MTS > SCMC > MRS > SA > TG > MGS > AV > AC; at 2% concentration, SCMC > MTS > SA > MRS > TG > MGS > AV > AC; at 3% concentration, SCMC > SA > TG > MTS > MRS > MGS > AV > AC.

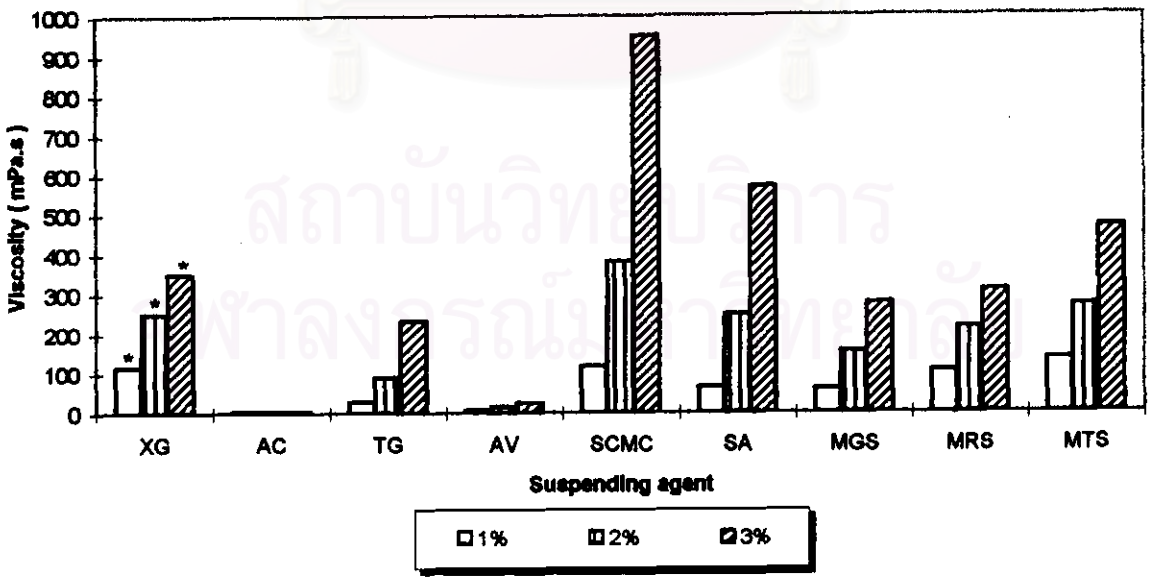
Table 22 Viscosity of Ibuprofen Suspension Containing Modified Starches as Suspending Agents at Varied Concentration - Evaluated in three Conditions

	Average Apparent Viscosity (mPas + SD)								
	MGS			MRS			MTS		
	Initial	Final-NC	Final-FT	Initial	Final-NC	Final-FT	Initial	Final-NC	Final-FT
1%	59.139	45.516	38.483	104.764	91.259	73.997	135.855	117.921	96.934
	(16.560)	(9.397)	(7.207)	(34.983)	(27.662)	(21.036)	(57.983)	(42.659)	(28.347)
2%	155.597	133.632	121.922	215.290	199.000	162.854	272.185	231.625	208.053
	(46.176)	(31.108)	(32.106)	(85.074)	(68.637)	(51.991)	(116.34)	(88.248)	(66.946)
3%	277.015	202.762	216.052	219.026	308.287	252.866	467.342	329.185	302.273
	(82.145)	(48.034)	(54.666)	(89.345)	(116.277)	(91.690)	(195.303)	(126.578)	(107.302)

MGS = Modified Glutinous Rice Starch
MRS = Modified Rice Starch
MTS = Modified Tapioca Starch

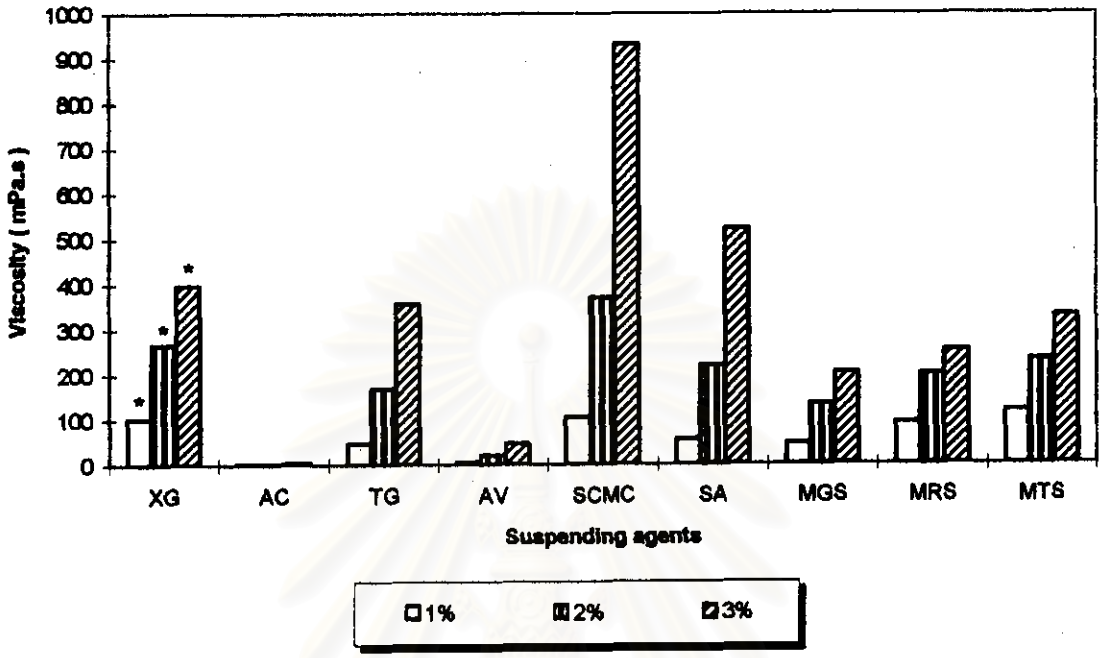
Initial = Newly Prepared Suspension
Final - NC = Normal Condition - After 12 weeks
Final - FT = Freeze-Thaw Treated Suspension

Figure 48 Comparative Viscosity of Ibuprofen Suspension Containing Varied Concentration of Suspending Agents - Initial Condition



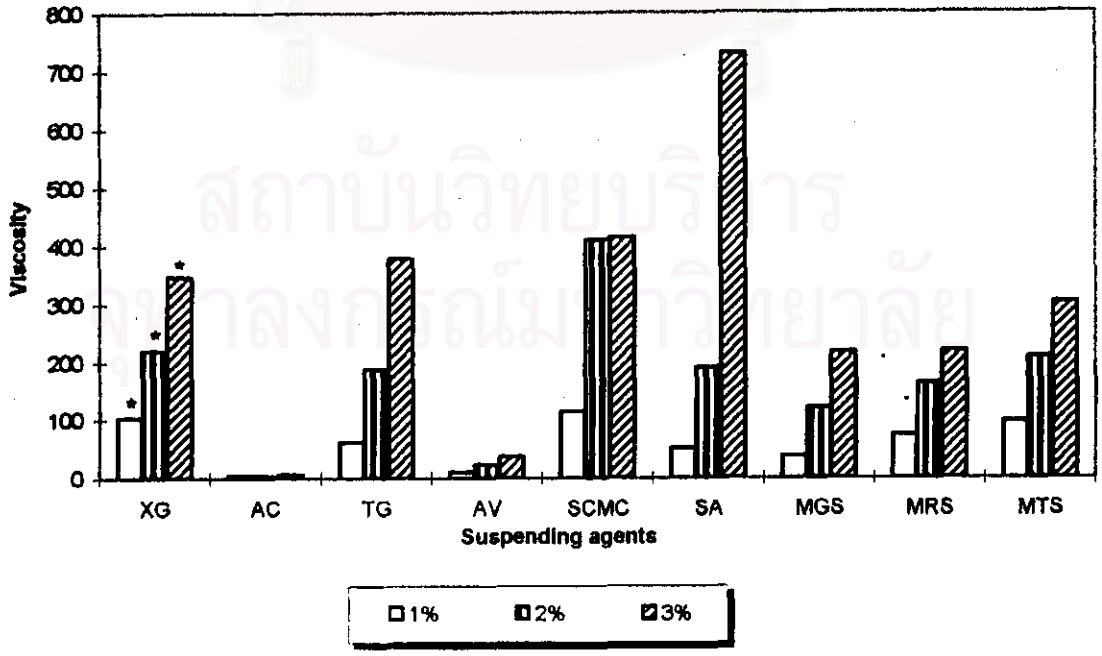
* used a different sensor (SV1)

Figure 49 Comparative Viscosity of Ibuprofen Suspension Containing Varied Concentration of Suspending Agents - Normal 12 weeks Condition



* used a different sensor (SV1)

Figure 50 Comparative Viscosity of Ibuprofen Suspension Containing Varied Concentration of Suspending Agents - FT Condition



* used a different sensor (SV1)

Figure 50 shows the viscosity of suspensions evaluated after FT treatment. The viscosity of suspensions from this condition was ranked in the following orders; at 1% concentration, SCMC > MTS > MRS > TG > SA > MGS > AV > AC; at 2% concentration, SCMC >MTS > SA > TG > MRS > MGS > AV > AC; at 3% concentration, SCMC > SA > TG > MTS > MRS > MGS > AV > AC.

The term viscosity calculated from an average of apparent viscosity of the upcurve and the downcurve (see Table 87, Appendix IV). It has been suggested that the higher the value, the better the suspending property. For overall evaluation of suspension in initial condition, the order of decreasing viscosity was XG > SCMC > MTS > SA > MRS > MGS > TG > AV > AC. After12 weeks, the order of decreasing viscosity was XG > SCMC > MTS > SA > MRS > TG > MGS > AV > AC. After FT treatment, the order of decreasing viscosity was XG > SCMC > MTS > SA > TG > MRS > MGS > AV > AC.

It should also be noted that the viscosity of XG was very high and was determined by an SV1 sensor which was different from the other suspending agents. The viscosity values obtained for XG were, therefore, uncomparable with those of other suspending agents. In this study XG was excluded from the comparison but was rather ranked as the most viscous compounds among all suspending agents used.

2.3.2 Thixotropy Measurement

Thixotropy is a rheological phenomenon which is described as a breakdown and reforming of the gel/sol/gel structure. It is a preferred property in the selection of suspending agent (Wood, 1986). Thixotropy can be quantitatively measured by several techniques and methods. Theoretically, suspending agent with higher the thixotropic value possessed better suspending property. In this study, the area of a so-called "hysteresis loop" which was the area between the upcurve and the downcurve of viscosity curve was employed to represent the value of thixotropy. The area was automatically integrated by a computer when the viscosity measurement was performed. However, since the area of hysteresis loop is very much dependent on the time taken to make the measurement as well as the maximum shear rate (Deem, 1988), the values of thixotropy obtained from the measurement with different sensor are sometimes not comparable. For example, XG was evaluated with SV1 sensor, which used a lower shear rate, could not be compared with MV sensor which used a higher shear rate.

The comparative flow curves of ibuprofen suspensions containing 1, 2, and 3% of modified starches evaluated in initial, normal 12 weeks, and FT conditions are shown in Figures 51-59. Each curve clearly exhibited pseudoplastic flow characteristic with thixotropy. Thixotropic quantity of each curve was calculated as a quantity of thixotropic breakdown. The results are presented in Figures 60-62. Regardless the type of modified starch and the condition used, thixotropic quantity increased when the

Figure 51 Comparative Flow Curves of Ibuprofen Suspension Containing 1% MRS Evaluated in Three Conditions

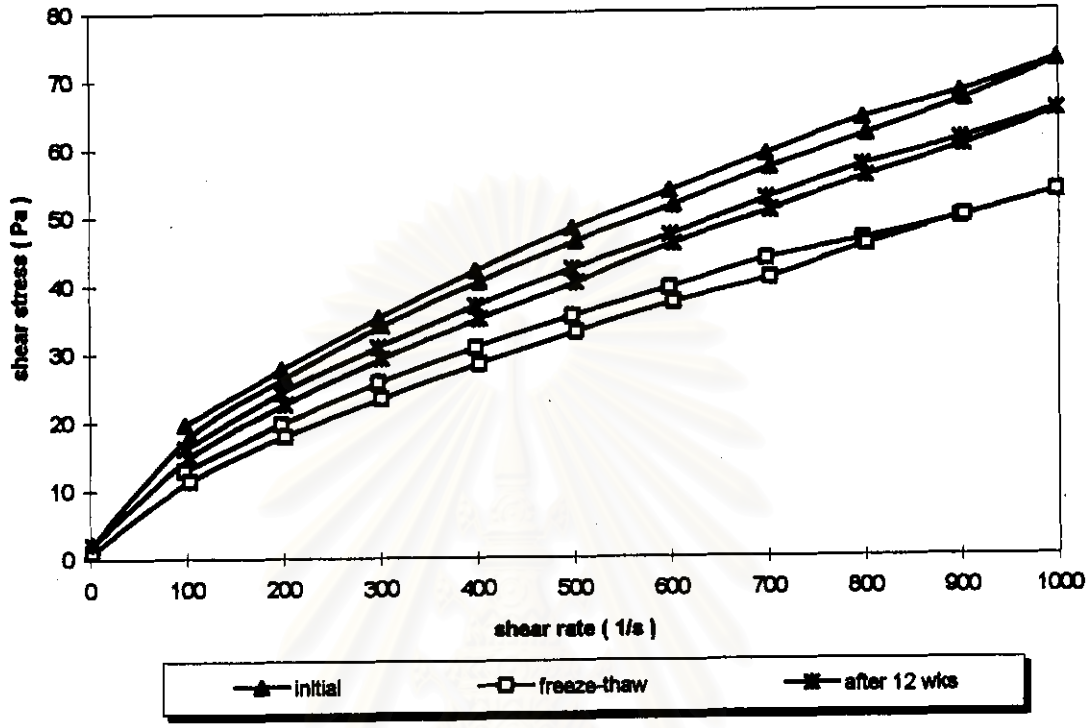


Figure 52 Comparative Flow Curves of Ibuprofen Suspension Containing 2% MRS Evaluated in Three Conditions

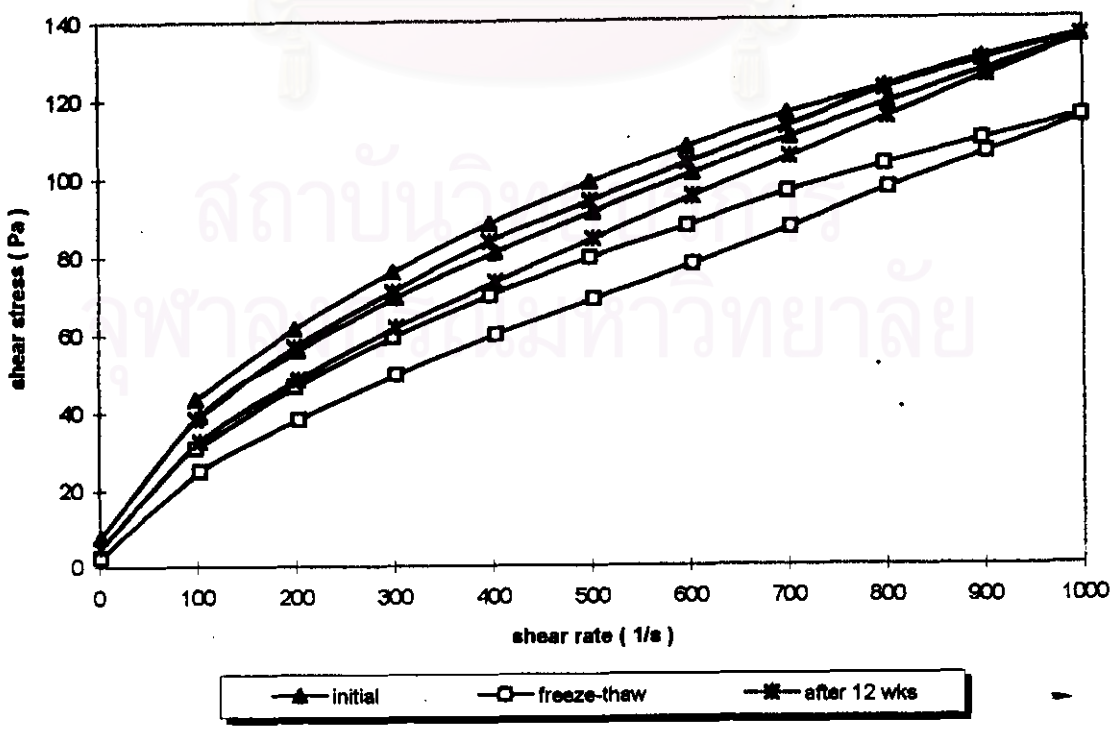


Figure 53 Comparative Flow Curves of Ibuprofen Suspension Containing 3% MRS Evaluated in Three Conditions

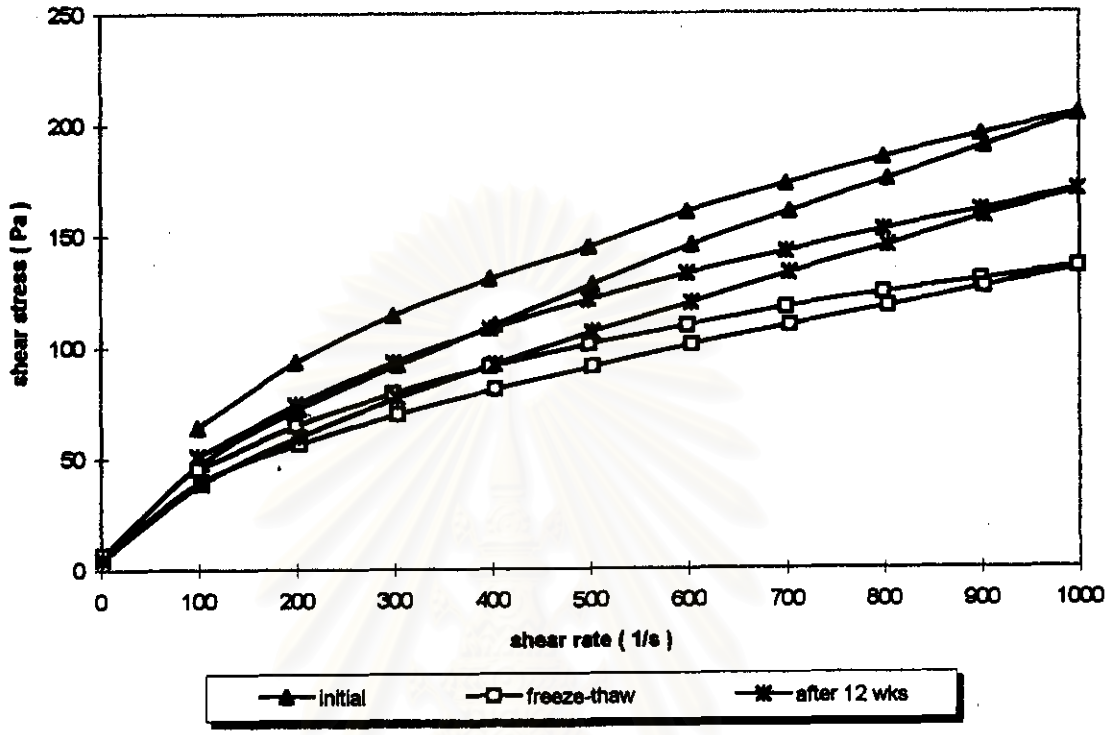


Figure 54 Comparative Flow Curves of Ibuprofen Suspension Containing 1% MTS Evaluated in Three Conditions

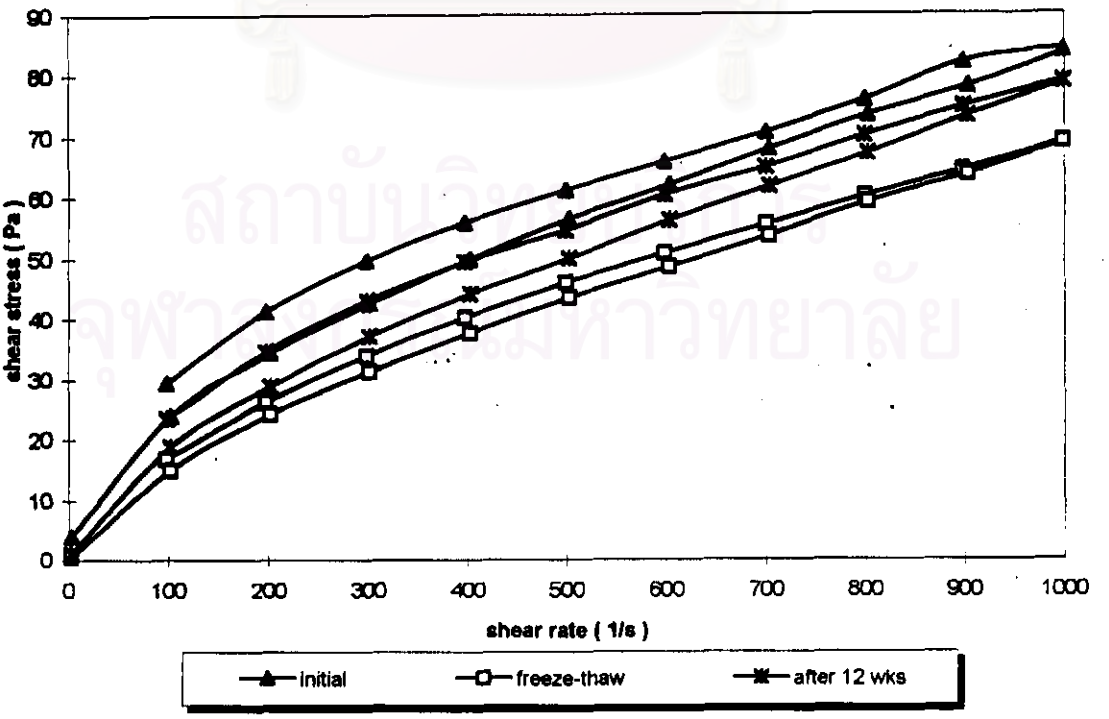


Figure 55 Comparative Flow Curves of Ibuprofen Suspension Containing 2% MTS Evaluated in Three Conditions

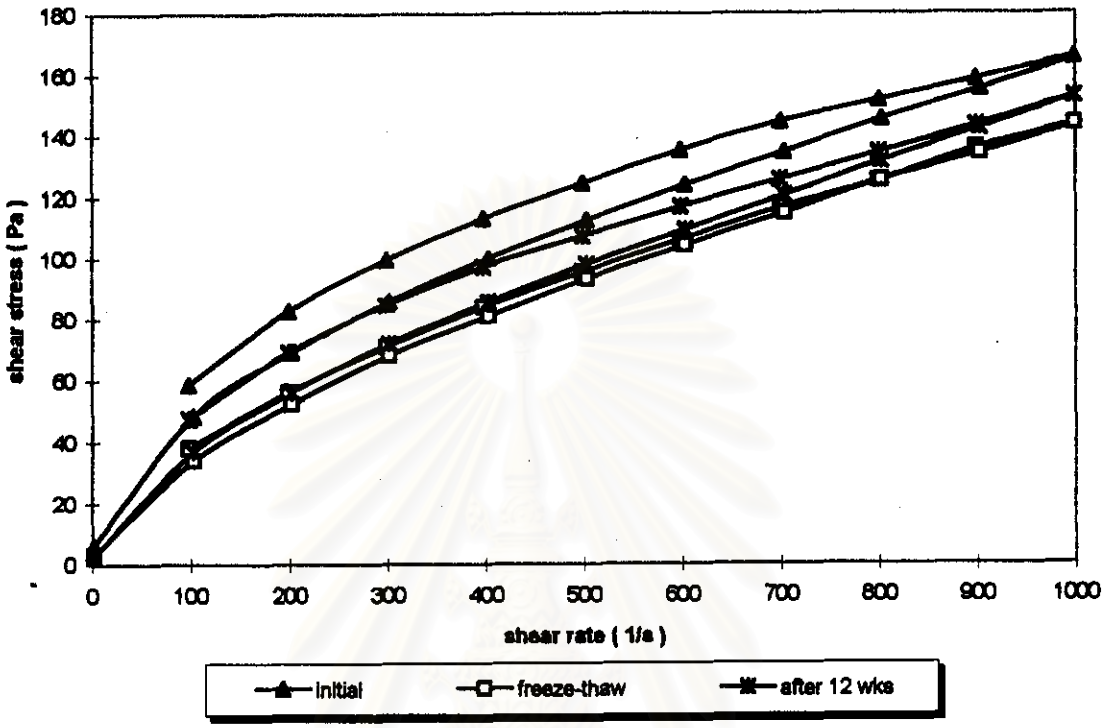


Figure 56 Comparative Flow Curves of Ibuprofen Suspension Containing 3% MTS Evaluated in Three Conditions

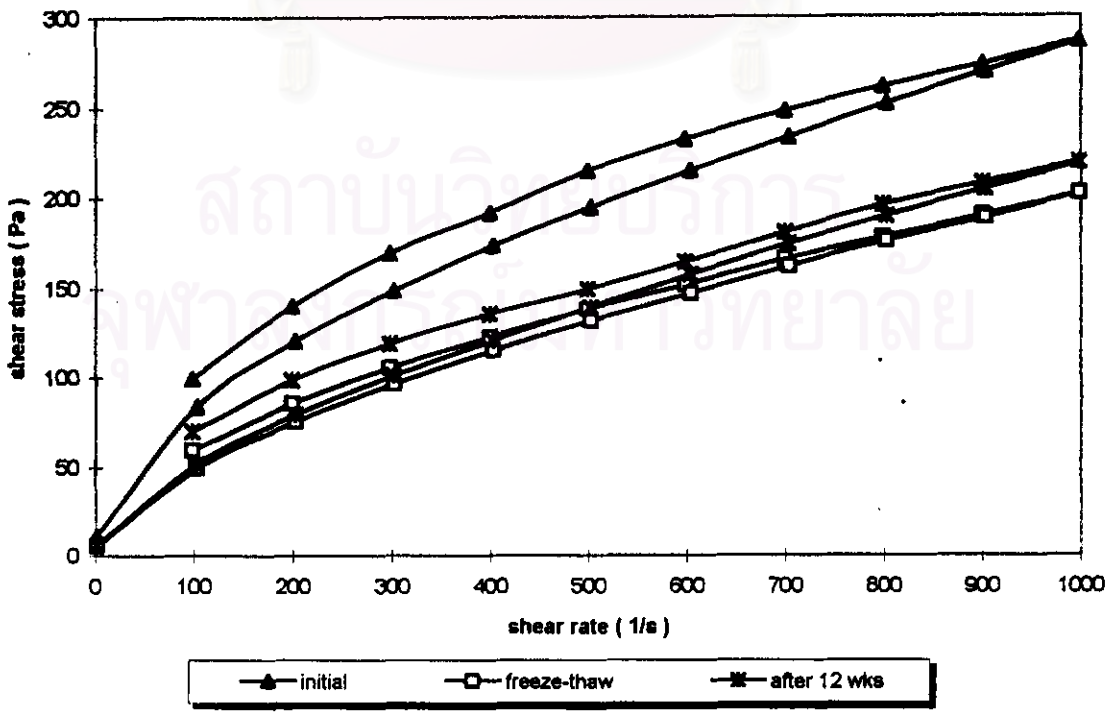


Figure 57 Comparative Flow Curves of Ibuprofen Suspension Containing 1% MGS Evaluated in Three Conditions

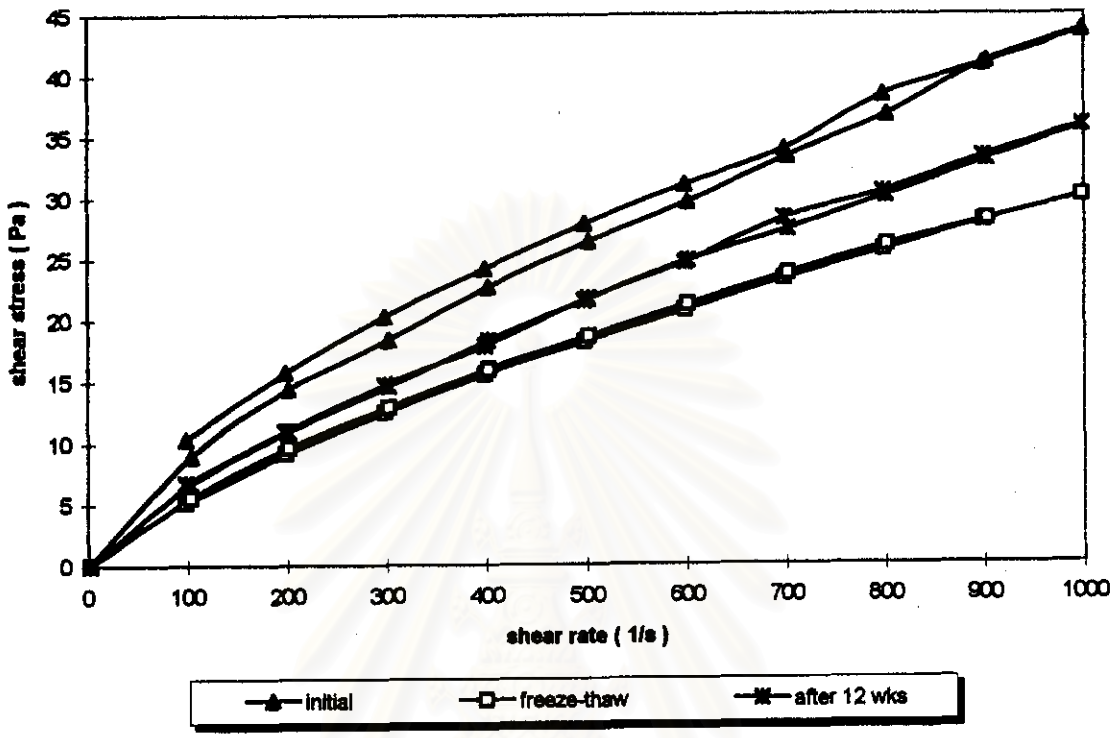


Figure 58 Comparative Flow Curves of Ibuprofen Suspension Containing 2% MGS Evaluated in Three Conditions

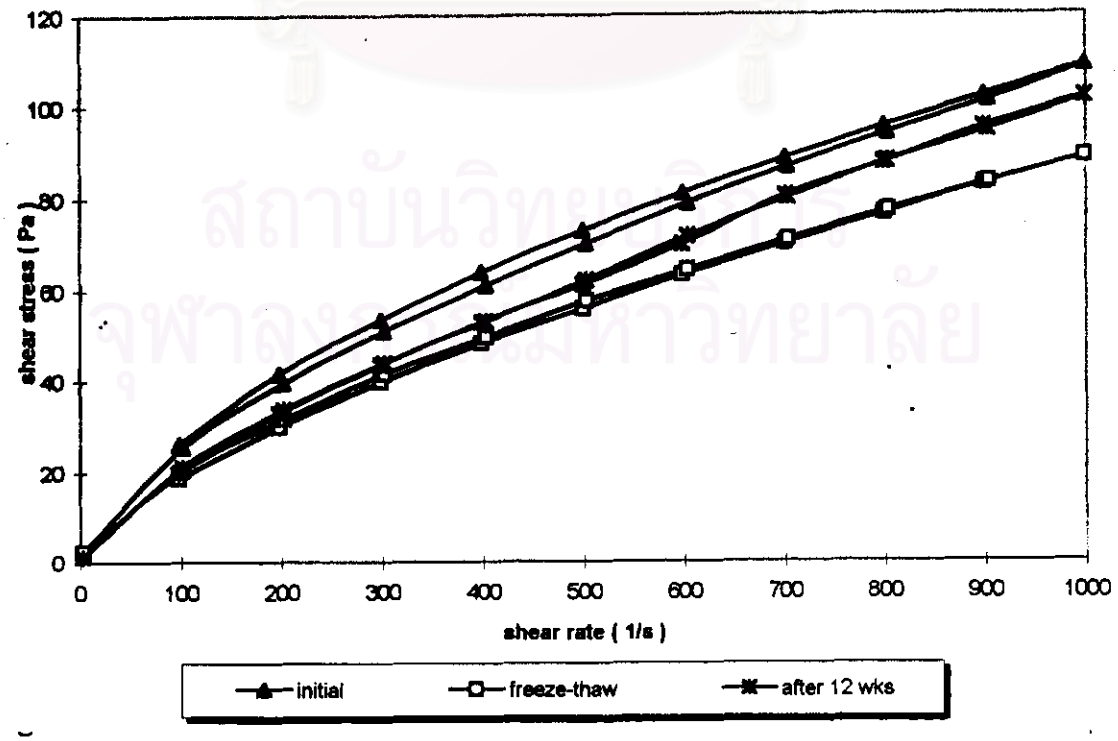


Figure 59 Comparative Flow Curves of Ibuprofen Suspension Containing 3% MGS Evaluated in Three Conditions

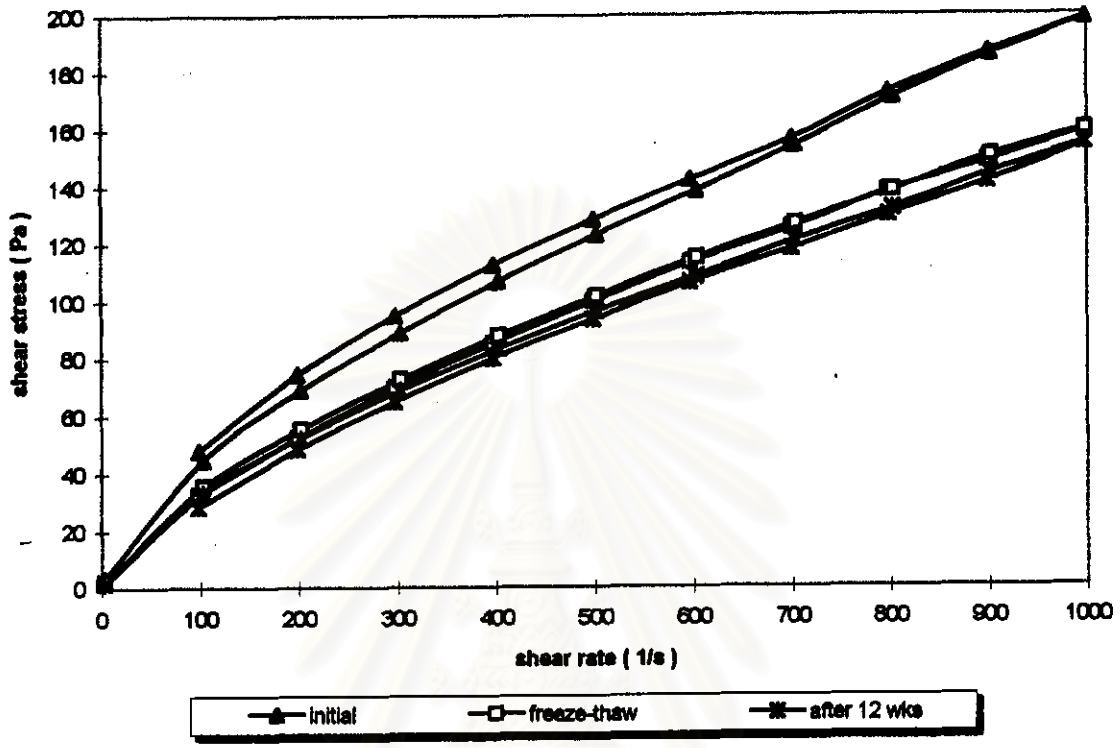


Figure 60 Comparative Thixotropic Quantities of Ibuprofen Suspension Containing 1, 2, and 3% of MRS Evaluated in 3 Conditions

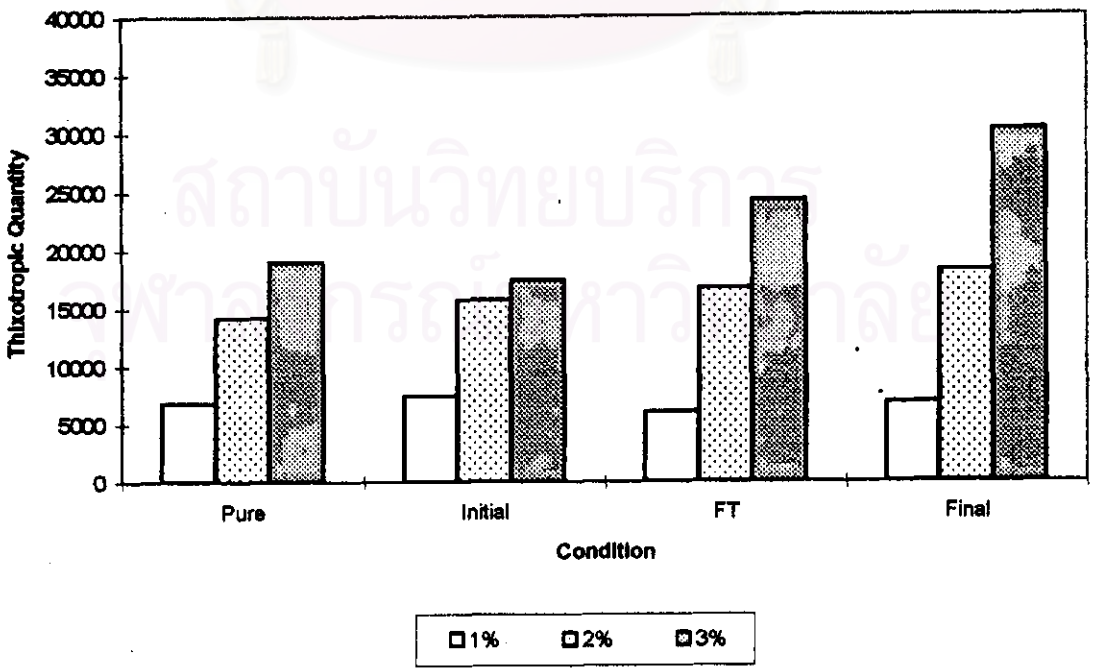


Figure 61 Comparative Thixotropic Quantities of Ibuprofen Suspension Containing 1, 2, and 3% of MGS Evaluated in 3 Conditions

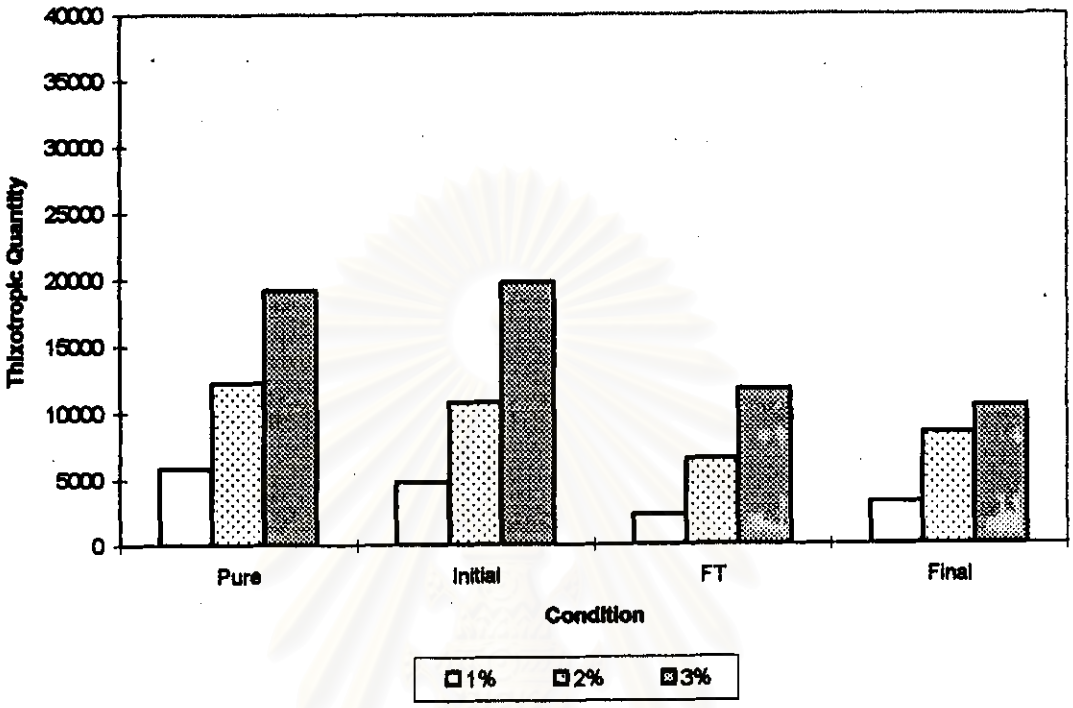
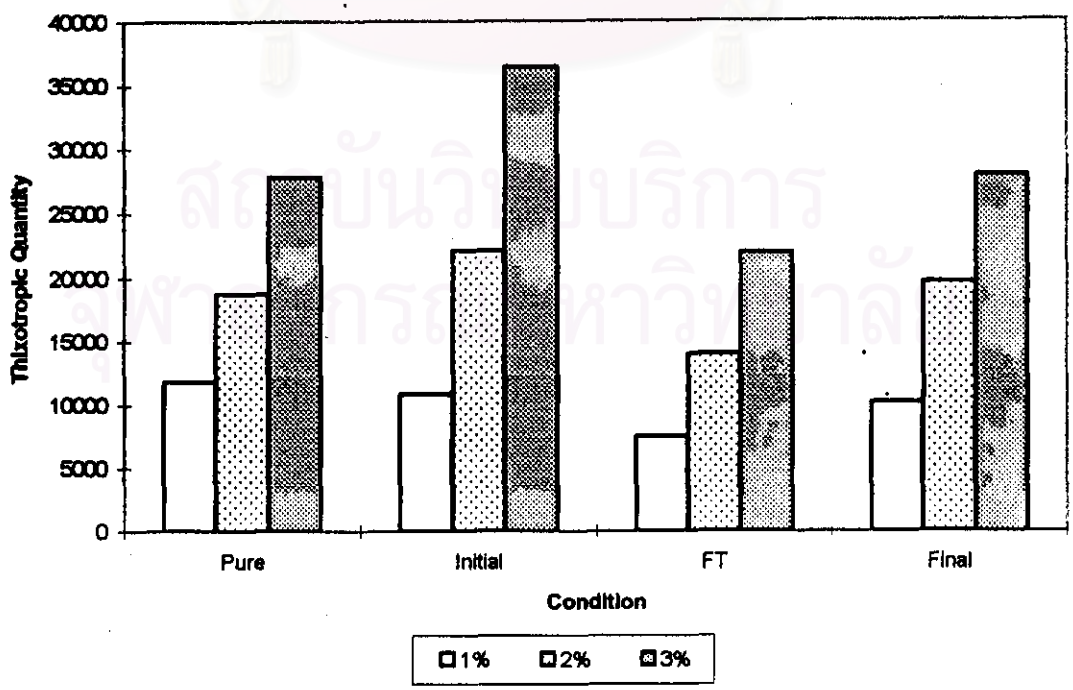


Figure 62 Comparative Thixotropic Quantities of Ibuprofen Suspension Containing 1, 2, and 3% of MTS Evaluated in 3 Conditions



concentration increased and the thixotropic quantity of initial suspension was similar to that of dispersion of suspending agent indicating that thixotropic quantity of suspension was exclusively contributed by suspending agent. The statistical differences among thixotropic quantity of modified starch containing ibuprofen suspensions ($p < 0.05$) are presented in Table 51-52, 53-54, and 55-56 (Appendix II) for MRS, MGS and MTS, respectively. For MRS, the statistical analysis indicated that no significant difference was observed among thixotropic quantities of inital, normal 12 weeks, and FT treated ibuprofen suspension. For MGS, the thixotropic quantity of normal 12 weeks and FT treated suspensions showed no significant difference from each other but were both significantly less than that of initial suspension. For MTS, thixotropic quantity of FT treated suspension was significantly different from that of the other two conditions. These results suggested that MRS was the most stable suspending agent among all three modified starches in this aspect.

The comparative flow curves of ibuprofen suspensions that contained three concentrations of suspending agents evaluated in three conditions are shown in Figure 63-71. The thixotropic quantity was determined and the comparative thixotropic quantities of ibuprofen suspensions are illustrated in Tables 23-25 and Figures 72-74. In initial condition, the thixotropic quantity was ranked in the following orders; at 1% concentration, MTS > SCMC > MRS > MGS > SA > TG > AV > AC; at 2% concentration, SCMC > MTS > MRS > SA > MGS > TG > AV > AC; at 3% concentration, MTS > SA > MGS > MRS > TG > AV > AC. After 12 weeks of storing, the order of thixotropic quantity of suspensions was; at 1% concentration,

Figure 63 Comparative Flow Curves of Ibuprofen Suspension Containing Varied Suspending Agent at Concentration 1% w/v - Initial Condition

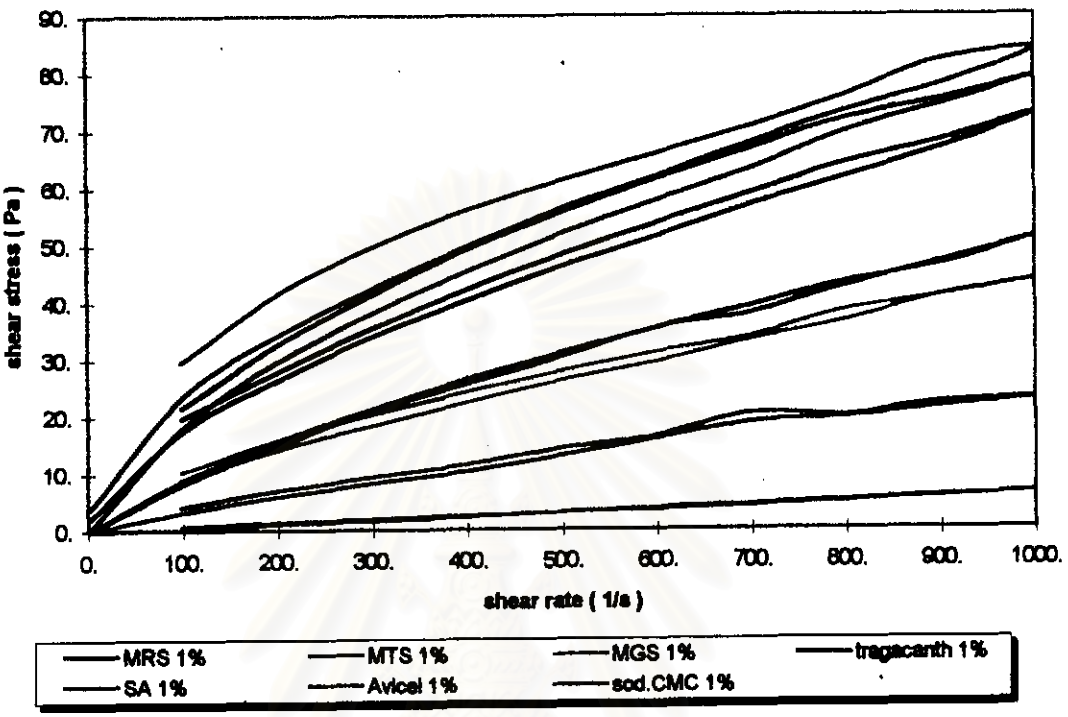


Figure 64 Comparative Flow Curves of Ibuprofen Suspension Containing Varied Suspending Agent at Concentration 2% w/v - Initial Condition

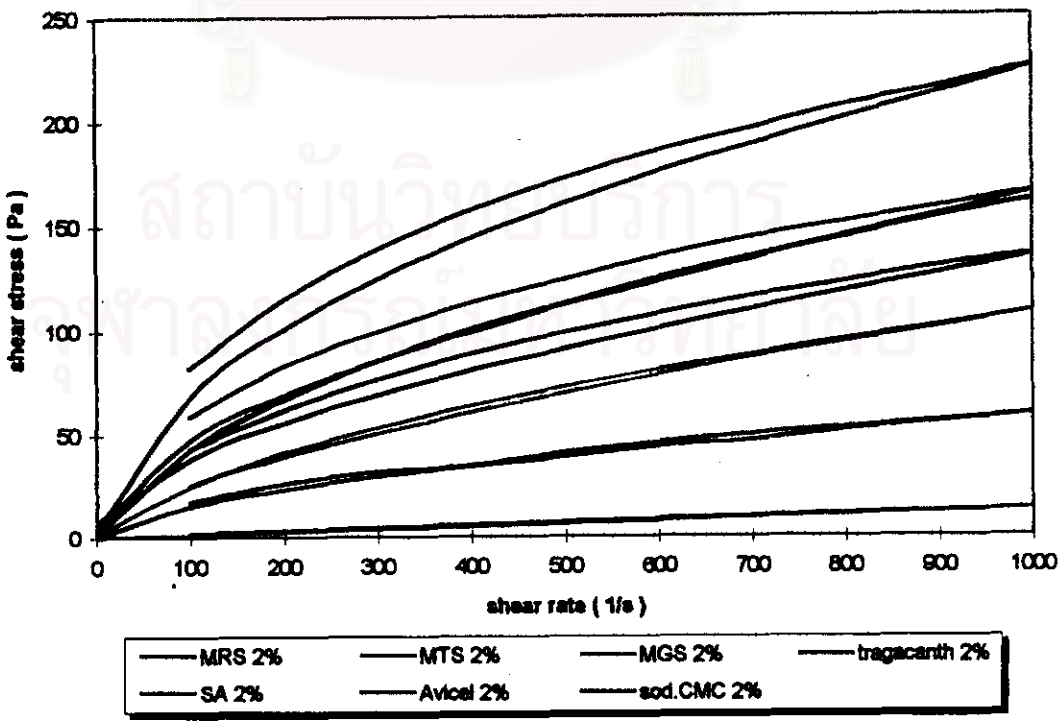


Figure 65 Comparative Flow Curves of Ibuprofen Suspension Containing Varied Suspending Agent at Concentration 3% w/v - Initial Condition

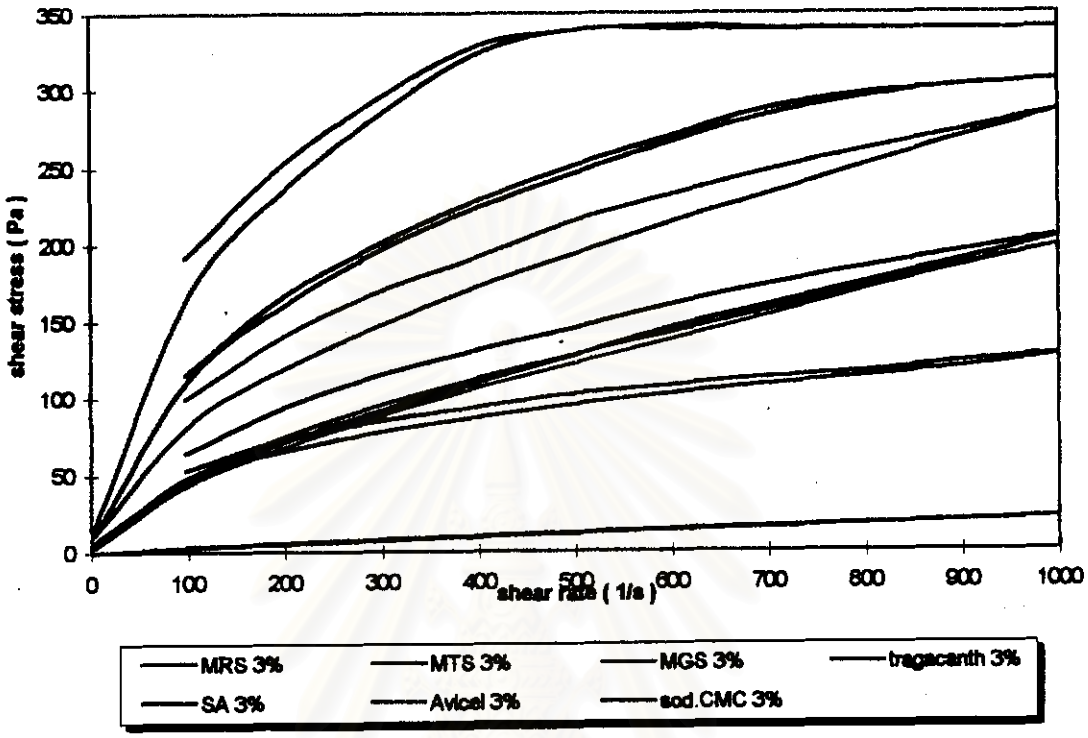


Figure 66 Comparative Flow Curves of Ibuprofen Suspension Containing Varied Suspending Agent at Concentration 1% w/v - After 12 weeks

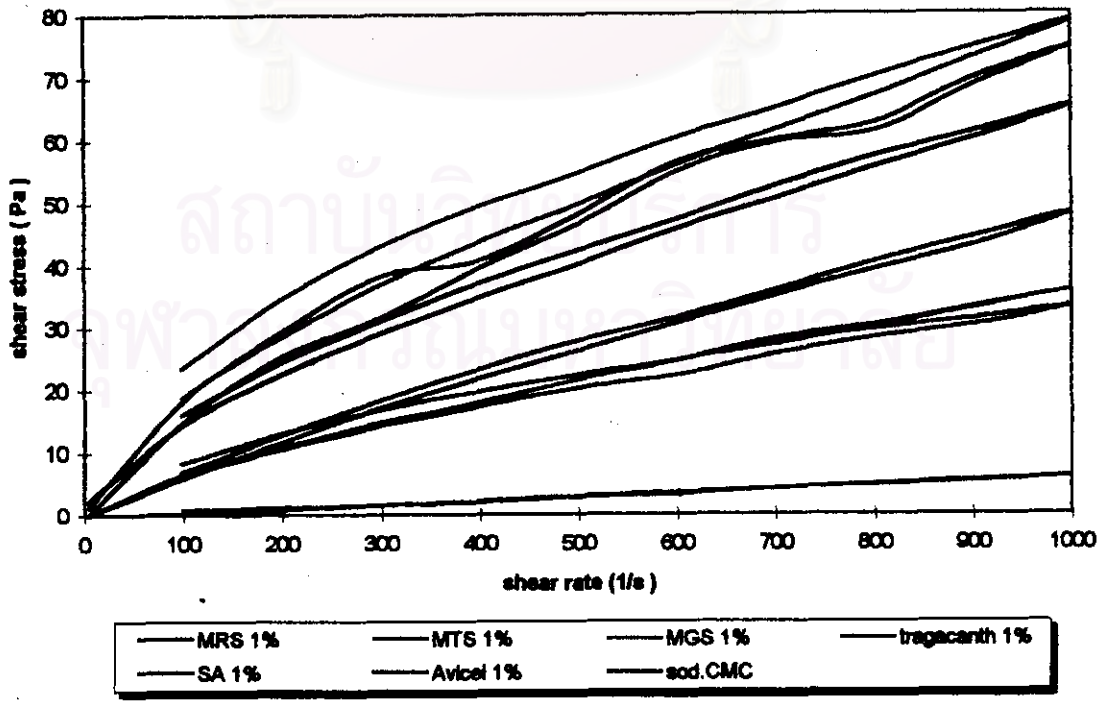


Figure 67 Comparative Flow Curves of Ibuprofen Suspension Containing Varied Suspending Agent at Concentration 2% w/v - After 12 weeks

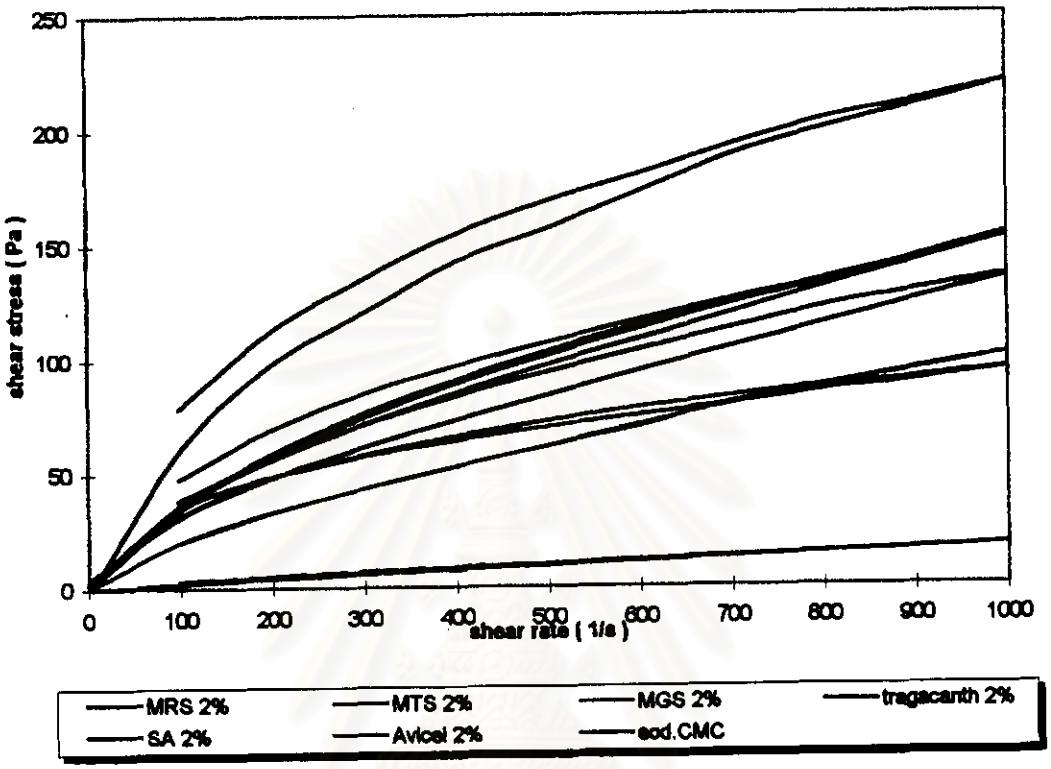


Figure 68 Comparative Flow Curves of Ibuprofen Suspension Containing Varied Suspending Agent at Concentration 3% w/v - After 12 weeks

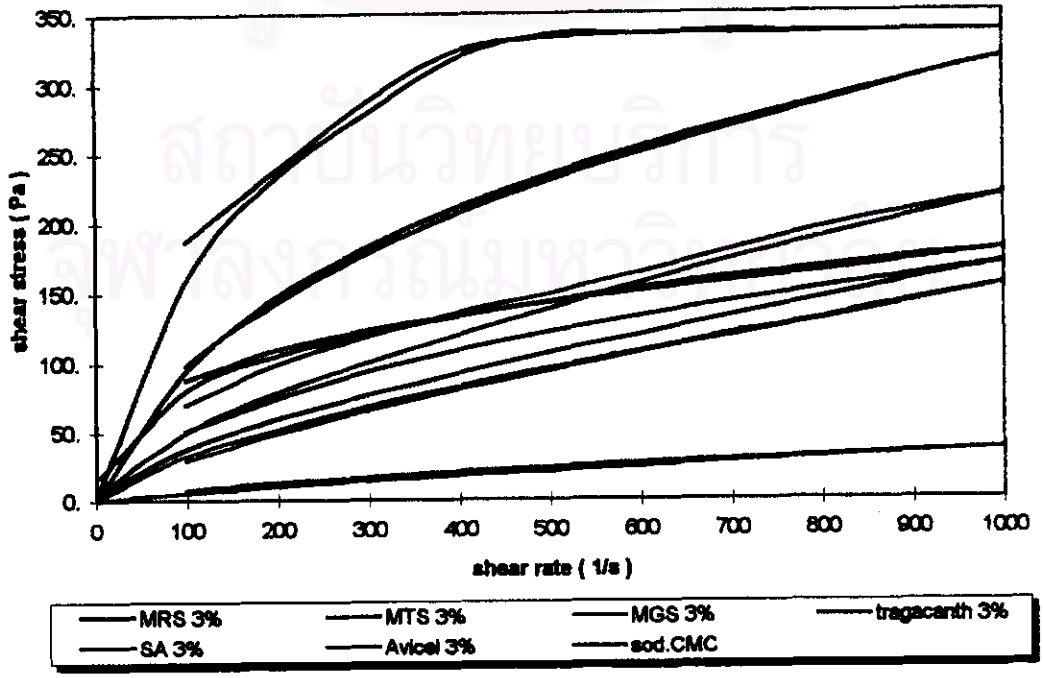


Figure 69 Comparative Flow Curves of Ibuprofen Suspension Containing Varied Suspending Agent at Concentration 1% w/v - FT Condition

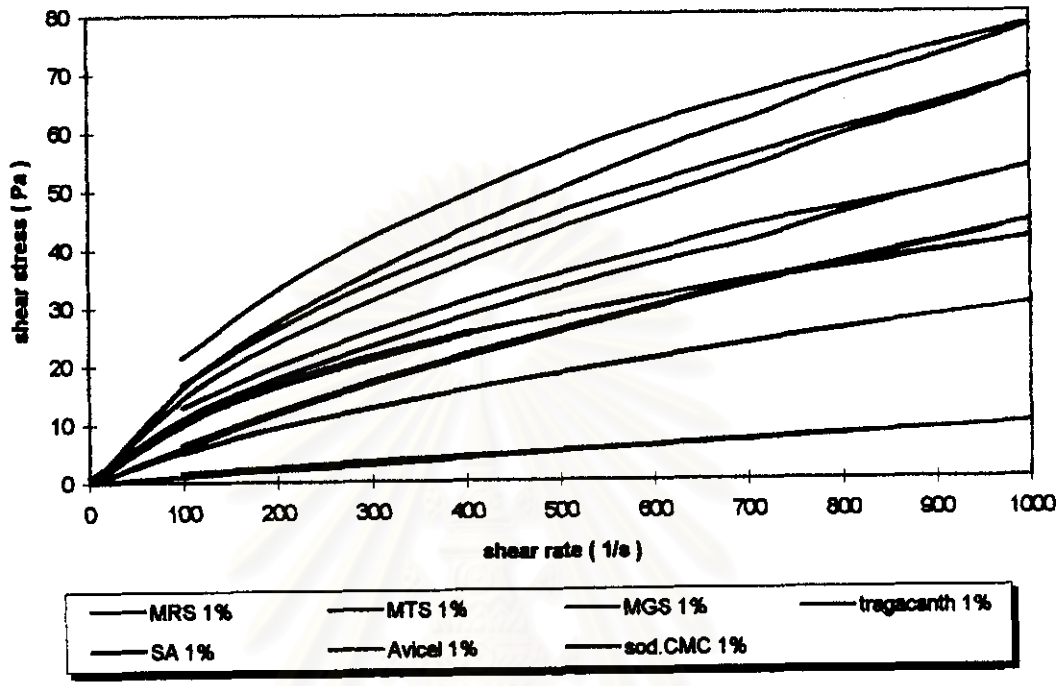


Figure 70 Comparative Flow Curves of Ibuprofen Suspension Containing Varied Suspending Agent at Concentration 2% w/v - FT Condition

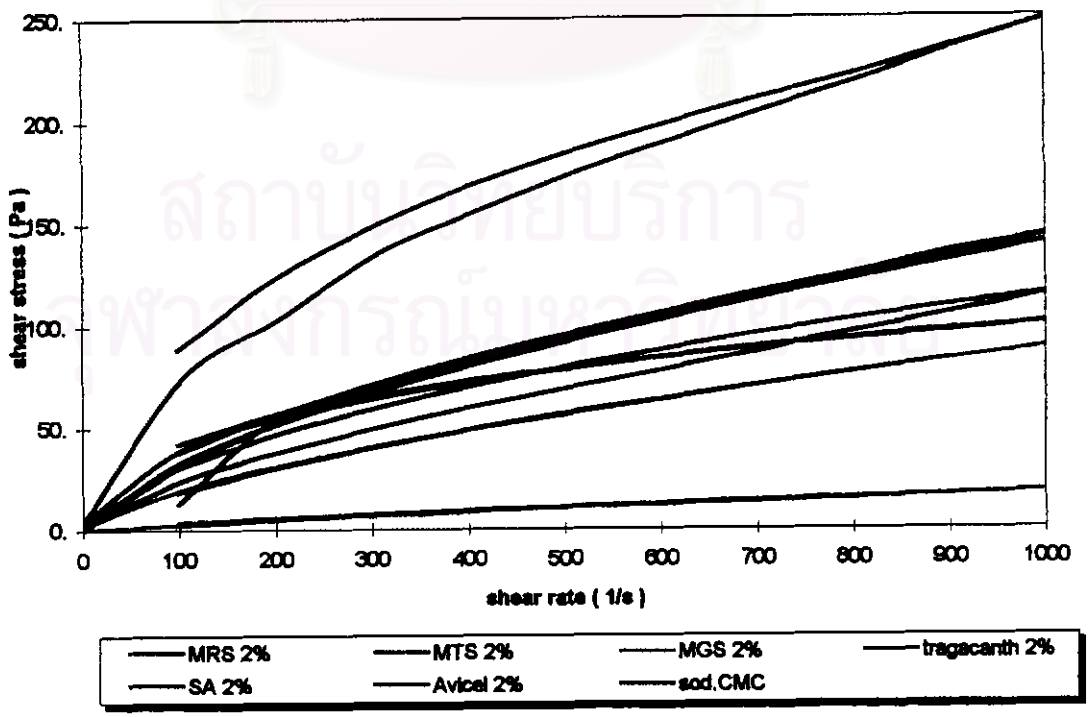


Figure 71 Comparative Flow Curves of Ibuprofen Suspension Containing Varied Suspending Agent at Concentration 3% w/v - FT Condition

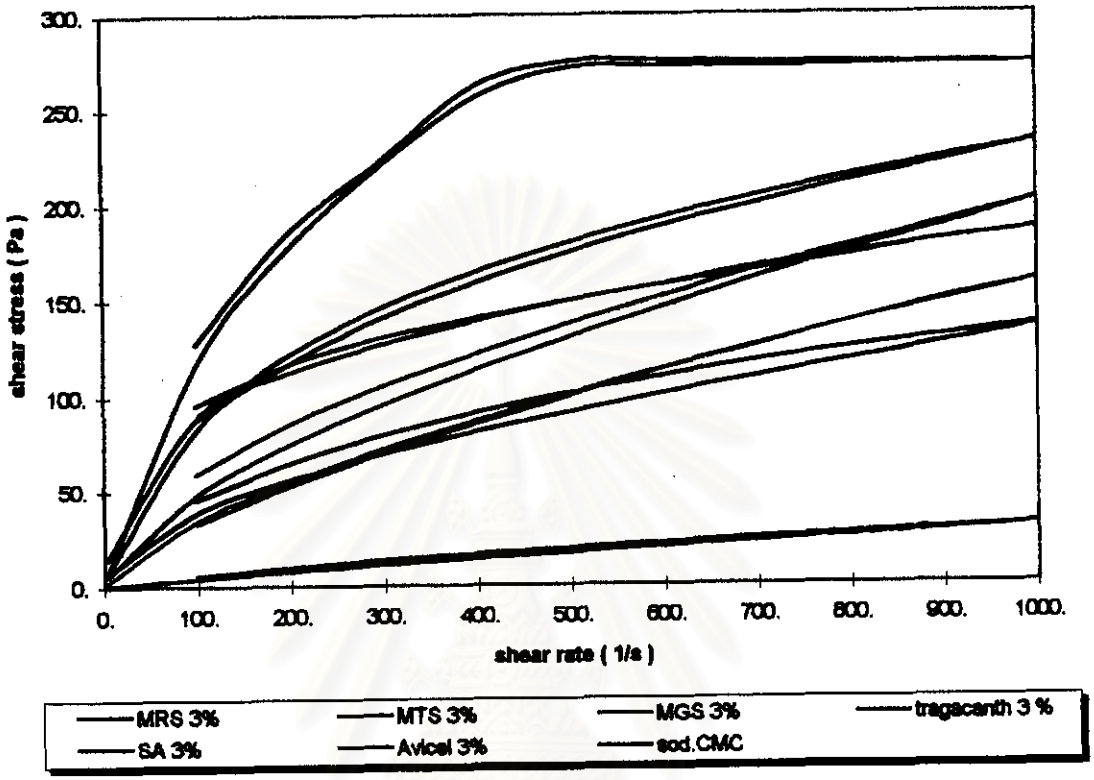
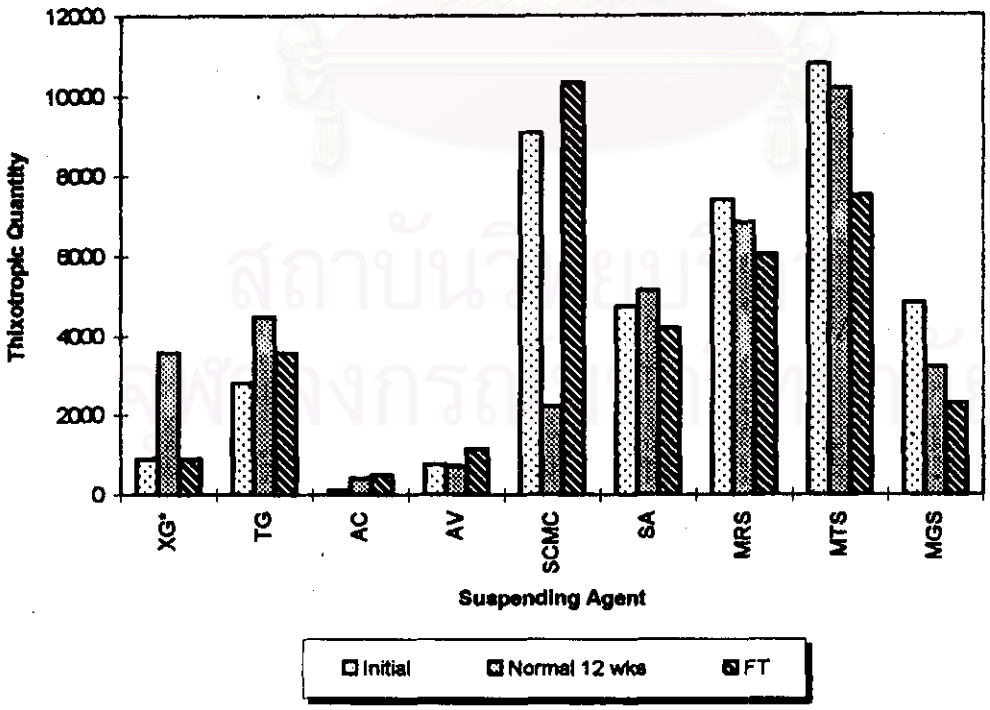


Table 23 Comparative Thixotropic Quantity of Ibuprofen Suspensions Containing 1% Suspending Agent

Suspending Agent	Condition		
	Initial	Normal 12 wks	FT
XG*	908	3581	906
TG	2810	4470	3560
AC	108	405	498
AV	778	730	1157
SCMC	9090	2227	10320
SA	4740	5130	4190
MRS	7390	6840	6030
MTS	10800	10200	7500
MGS	4820	3220	2300

Figure 72 Comparative Thixotropic Quantity of Ibuprofen Suspensions Containing 1% Suspending Agent

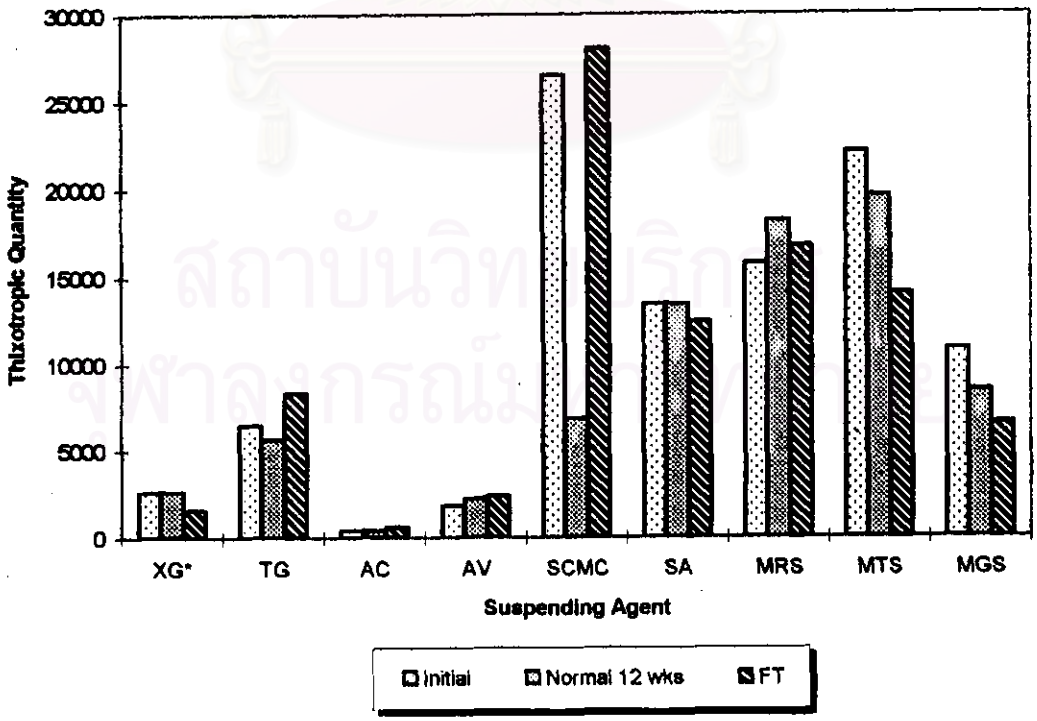


* determined by a different sensor (SV1)

Table 24 Comparative Thixotropic Quantity of Ibuprofen Suspensions Containing 2% Suspending Agent

Suspending Agent	Condition		
	Initial	Normal 12 wks	FT
XG*	2633	2614	1570
TG	6460	5650	8340
AC	434	431	600
AV	1846	2252	2371
SCMC	26500	6850	28000
SA	13390	13410	12390
MRS	15720	18190	16690
MTS	22060	19600	14000
MGS	10810	8450	6550

Figure 73 Comparative Thixotropic Quantity of Ibuprofen Suspensions Containing 2% Suspending Agent

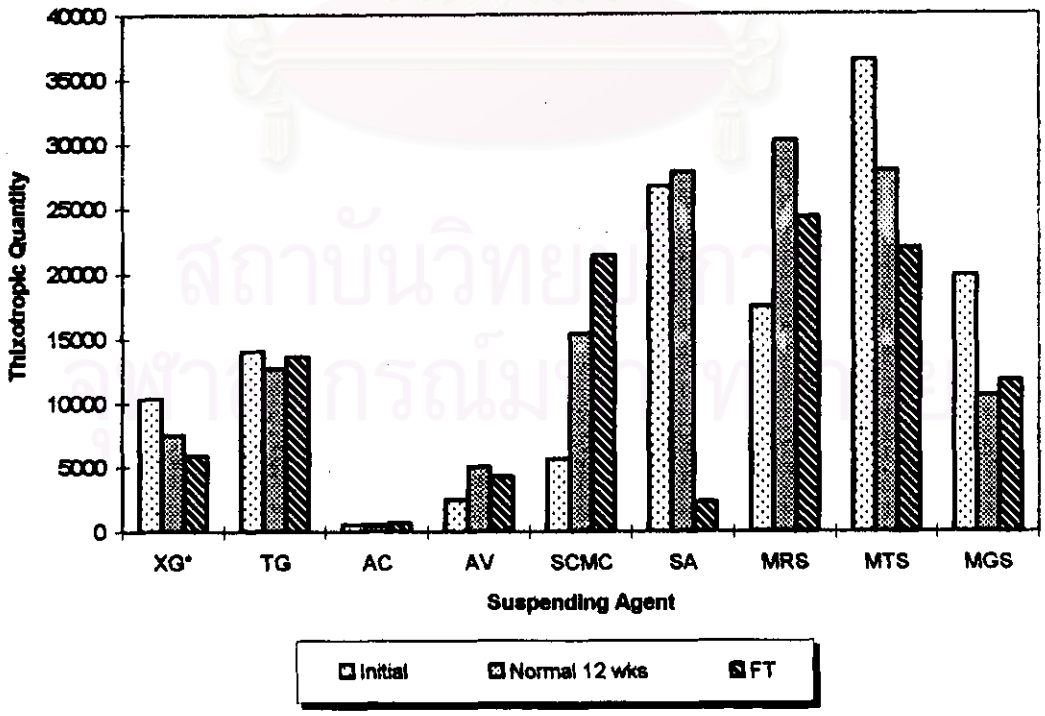


* determined by a different sensor (SV1)

Table 25 Comparative Thixotropic Quantity of Ibuprofen Suspensions Containing 3% Suspending Agent

Suspending Agent	Condition		
	Initial	Normal 12 wks	FT
XG*	10350	7508	5880
TG	14020	12700	13600
AC	532	523	670
AV	2498	4990	4240
SCMC	5608	15350	21300
SA	26700	27800	2284
MRS	17430	30200	24230
MTS	36400	27900	21900
MGS	19800	10510	11730

Figure 74 Comparative Thixotropic Quantity of Ibuprofen Suspensions Containing 3% Suspending Agent



* determined by a different sensor (SV.1)

MTS > MRS > SA > TG > MGS > SCMC > AV > AC, at 2% concentration, MTS > MRS > SA > MGS > SCMC > TG > AV > AC, at 3% concentration, MRS > MTS > SA > SCMC > TG > MGS > AV > AC. Overall consideration, the value can be ranked in the following order; MTS > MRS > SA > SCMC > TG > MGS > AV > AC. For FT treated suspensions, the order is; at 1% concentration, SCMC > MTS > MRS > SA > TG > MGS > AV > AC, at 2% concentration, SCMC > MRS > MTS > SA > TG > MGS > AV > AC, at 3% concentration, MRS > MTS > SCMC > TG > MGS > AV > AC. The overall order of decreasing thixotropic value for FT evaluation was SCMC > MRS > MTS > SA > TG > MGS > AV > AC.

The results showed that modified starches, especially MTS and MRS, possessed high thixotropic quantity in both conditions comparable to that of SCMC and SA, and the values were much more than that of AV and AC. Again, from thixotropic value point of view MTS and MRS are as good suspending agents as SCMC and SA.

Although the values of both viscosity and thixotropic quantity of ibuprofen suspensions evaluated in FT condition were generally lower than those obtained from normal 12 weeks evaluation, statistical analyses showed that the differences were not significant. This results indicated that FT treated suspensions, especially those contained MRS and MTS, were still highly stable despite the fact that they have been exposed to a more stress condition than those in normal condition. At all tested

concentrations, MTS containing suspension possessed the highest values in both viscosity and thixotropic quantity among three modified starch containing suspensions.

Freeze-thaw evaluation is a preocess designed for aging test. The process is simply a cyclic temperature testing of repeated freezing and thawing for short periods of storage to test for physical stability. The advantage of this stressful test is that the preparation can be assumed to have good physical stability during prolonged storage at ambient temperature if it is able to withstand exposure to extremes in temperature (Nash, 1988). The results obtained from FT evaluation and normal storage evaluation provide useful information in the prediction of suspension stability. In this study, the comparable results, especially for suspensions containing MTS and MRS, obtained from both conditions on all evaluation parameters suggested that these suspensions had a satisfactory stability overa wide range of storaging condition. The change in temperature in FT cycle had almost no different effects on MRS containing suspensions compared to those evaluated in normal condition.

2.4 Study on Uniformity of Drug Dispersion During Storage

2.4.1 Preparation of Standard Curve

Standard curve for UV determination of ibuprofen was successfully established by measuring the absorbance of five concentrations of ibuprofen solution. The measurement was performed at 223 nm, a λ_{max} of ibuprofen, using phosphate buffer pH 7.2 as a blank. The absorbance data and the standard curve are shown in Table 36

and Figure 82 (Appendix I). The range of absorbance obtained from this measurement was between 0.00 and 1.50.

From the regression analysis, a correlation coefficient of 0.9999 was obtained for the established standard curve indicating an almost linear relationship between the absorbance and the concentration of ibuprofen. The equation deduced from the analysis was;

$$Y = 0.41778X + 0.00352$$

where Y = Absorbance

X = Concentration of Ibuprofen (g/100 mL)

2.4.2 Determination of Uniformity of Ibuprofen Dispersion During Storage

Ibuprofen content of each sample of 14 suspensions which showed good sedimentaiton volume was determined by using standard curve. The suspensions were those contained 1,2,3% XG, 1,2,3% MTS, 1,2,3% MRS, 2,3% SCMC, 2,3%MGS, and 3% TG. The results are shown in Tables 26-33 for those contained MS and in Tables 37-42 (Appendix I) for those contained other suspending agents. For each suspension, a triplicate result of ibuprofen content determining from three different depth levels of test tubes was reportedd every two weeks over a period of 12 weeks.

The uniformity of ibuprofen suspension during storage was determined by calculating the deviation of ibuprofen concentrations obtained from three different

Table 26 Ibuprofen Contents (g/100 mL) Found at Different Locations of Test Tubes Containing Ibuprofen Suspension with 1% MTS as Suspending Agent

Sampling Point	Ibuprofen Content (g/100mL)						
(Location-Tube)	Week 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Top-1	1.9902	1.9854	1.9735	1.9639	1.9448	1.9471	1.9759
Middle-1	1.9783	1.9759	1.9998	2.0070	1.9950	1.9687	1.9878
Bottom-1	1.9974	2.0022	2.0214	1.9998	2.0237	2.0453	2.0668
Top-2	2.0022	2.0046	1.9663	1.9543	1.9304	1.9256	1.9304
Middle-2	1.9783	2.0285	2.0190	1.9831	1.9783	2.0022	2.0046
Bottom-2	2.0214	2.0285	2.0429	2.0214	2.0501	2.0596	2.0381
Top-3	1.9735	1.9902	1.9878	1.9400	1.9639	1.9591	1.9615
Middle-3	2.0070	2.0118	1.9974	2.0261	1.9663	1.9950	1.9352
Bottom-3	1.9950	2.0190	2.0309	2.0668	1.9998	2.0237	2.0788

Table 27 Ibuprofen Contents (g/100 mL) Found at Different Locations of Test Tubes Containing Ibuprofen Suspension with 2% MTS as Suspending Agent

Sampling Point	Ibuprofen Content (g/100mL)						
(Location-Tube)	Week 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Top-1	1.9591	1.9256	1.9424	1.8753	1.9017	1.8825	1.9089
Middle-1	1.9280	1.9567	1.9136	1.9471	1.9519	1.9400	1.9495
Bottom-1	1.9328	1.9663	1.9519	1.9639	2.0118	2.0022	2.0381
Top-2	1.9735	1.9448	1.9112	1.9280	1.9160	1.9352	1.8801
Middle-2	1.9471	1.9160	1.9256	1.9136	1.9280	1.9663	1.9280
Bottom-2	1.9208	1.9424	1.9711	1.9854	2.0477	2.0142	1.9807
Top-3	1.9519	1.9352	1.8993	1.9328	1.8562	1.9208	1.8993
Middle-3	1.9352	1.9448	1.8801	1.9591	1.9567	1.9615	1.9711
Bottom-3	1.9615	1.9519	1.9615	1.9184	1.9831	1.9950	2.0261

Table 28 Ibuprofen Contents (g/100 mL) Found at Different Locations of Test Tubes Containing Ibuprofen Suspension with 3% MTS as Suspending Agent

Sampling Point (Location-Tube)	Ibuprofen Content (g/100mL)						
	Week 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Top-1	1.9902	1.9735	2.0070	1.9759	1.9926	1.9639	1.9998
Middle-1	1.9759	1.9878	1.9759	1.9926	1.9831	2.0022	1.9950
Bottom-1	1.9783	1.9926	2.0094	1.9783	2.0094	2.0261	2.0285
Top-2	1.9998	1.9591	1.9567	1.9854	2.0046	1.9448	1.9328
Middle-2	2.0118	1.9759	1.9807	1.9998	1.9519	1.9711	1.9998
Bottom-2	1.9902	2.0261	1.9711	1.9998	1.9878	2.0190	2.0094
Top-3	1.9735	1.9950	1.9854	2.0022	2.0118	1.9807	1.9639
Middle-3	1.9974	1.9998	1.9854	2.0166	2.0190	1.9926	2.0166
Bottom-3	1.9711	2.0118	1.9878	2.0285	2.0237	1.9998	1.9950

Table 29 Ibuprofen Contents (g/100 mL) Found at Different Locations of Test Tubes Containing Ibuprofen Suspension with 1% MRS as Suspending Agent

Sampling Point (Location-Tube)	Ibuprofen Content (g/100mL)						
	Week 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Top-1	1.9902	1.9304	1.9184	1.9065	1.8825	1.8753	1.8945
Middle-1	1.9759	1.9735	1.9543	1.9495	1.9663	1.9184	1.9639
Bottom-1	1.9783	1.9902	1.9950	2.0118	2.0261	2.0190	1.9974
Top-2	1.9998	1.9471	1.9256	1.9184	1.8897	1.9017	1.9041
Middle-2	2.0118	1.9783	1.9663	1.9663	1.9783	1.9352	1.9807
Bottom-2	1.9902	1.9854	2.0022	1.9974	1.9902	1.9998	2.0190
Top-3	1.9735	1.9232	1.9304	1.8897	1.9065	1.8945	1.9352
Middle-3	1.9974	1.9639	1.9280	1.9759	1.9902	1.9615	1.9902
Bottom-3	1.9711	1.9974	2.0214	2.0237	2.0237	2.0381	2.0070

Table 30 Ibuprofen Contents (g/100 mL) Found at Different Locations of Test Tubes Containing Ibuprofen Suspension with 2% MRS as Suspending Agent

Sampling Point	Ibuprofen Content (g/100mL)						
(Location-Tube)	Week 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Top-1	1.9783	1.9471	1.9591	1.9543	1.9304	1.9519	1.9232
Middle-1	1.9687	1.9974	1.9974	1.9831	1.9878	1.9902	1.9854
Bottom-1	1.9950	1.9615	1.9878	1.9998	2.0094	1.9926	2.0405
Top-2	1.9902	1.9519	1.9400	1.9424	1.9471	1.9208	1.9424
Middle-2	2.0070	1.9831	2.0142	2.0022	2.0046	2.0261	1.9998
Bottom-2	1.9759	1.9831	1.9759	2.0142	2.0214	2.0477	2.0309
Top-3	1.9974	1.9783	1.9519	1.9711	1.9256	1.9615	1.9639
Middle-3	1.9807	1.9759	1.9998	2.0070	2.0142	2.0190	2.0190
Bottom-3	2.0022	1.9902	2.0214	2.0357	2.0285	2.0118	2.0237

Table 31 Ibuprofen Contents (g/100 mL) Found at Different Locations of Test Tubes Containing Ibuprofen Suspension with 3% MRS as Suspending Agent

Sampling Point	Ibuprofen Content (g/100mL)						
(Location-Tube)	Week 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Top-1	1.9950	1.9591	1.9543	1.9543	1.9495	1.9615	1.9280
Middle-1	1.9783	1.9807	1.9950	1.9831	1.9735	2.0022	1.9974
Bottom-1	1.9807	1.9663	1.9974	1.9902	2.0022	2.0142	2.0070
Top-2	2.0070	1.9759	1.9400	1.9735	1.9663	1.9663	1.9471
Middle-2	1.9735	1.9854	2.0022	2.0022	2.0070	1.9807	2.0166
Bottom-2	1.9711	1.9878	1.9902	2.0070	2.0142	1.9950	2.0142
Top-3	1.9998	1.9711	1.9615	1.9280	1.9567	1.9831	1.9735
Middle-3	2.0118	1.9974	1.9926	1.9950	1.9950	1.9974	1.9854
Bottom-3	1.9902	1.9926	1.9878	1.9759	2.0429	2.0285	2.0214

Table 32 Ibuprofen Contents (g/100 mL) Found at Different Locations of Test Tubes Containing Ibuprofen Suspension with 2% MGS as Suspending Agent

Sampling Point (Location-Tube)	Ibuprofen Content (g/100mL)						
	Week 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Top-1	2.0333	1.2626	0.8341	0.4751	0.2621	0.2261	0.1783
Middle-1	2.0261	1.4349	1.1860	0.6259	0.4344	0.3363	0.2716
Bottom-1	2.0333	2.2200	2.6604	2.9908	3.4671	4.0248	4.2570
Top-2	2.0166	1.2315	0.8509	0.4823	0.2956	0.1807	0.1639
Middle-2	2.0309	1.4756	1.1932	0.6498	0.4559	0.2860	0.3147
Bottom-2	2.0405	2.2846	2.6724	2.9764	3.4336	3.7615	3.8931
Top-3	2.0429	1.2243	0.8150	0.4942	0.2333	0.1950	0.2022
Middle-3	2.0118	1.4158	1.2003	0.6091	0.4942	0.2740	0.3027
Bottom-3	2.0214	2.2583	2.8519	2.9573	3.4455	3.6322	3.5461

Table 33 Ibuprofen Contents (g/100 mL) Found at Different Locations of Test Tubes Containing Ibuprofen Suspension with 3% MGS as Suspending Agent

Sampling Point (Location-Tube)	Ibuprofen Content (g/100mL)						
	Week 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Top-1	1.9902	1.2410	0.8341	0.5972	0.2908	0.2118	0.2142
Middle-1	2.0118	1.3942	1.1860	0.7073	0.4679	0.2261	0.1376
Bottom-1	2.0453	2.2200	2.6604	3.0506	3.3187	3.8931	4.1995
Top-2	2.0099	1.2051	0.8509	0.5325	0.3003	0.2716	0.1950
Middle-2	2.0070	1.4589	1.1932	0.6498	0.6235	0.2094	0.2118
Bottom-2	2.0525	2.2499	2.6724	3.0195	3.3905	4.1277	3.7854
Top-3	2.0333	1.2147	0.8150	0.6570	0.2573	0.1902	0.1639
Middle-3	1.9998	1.6336	1.2003	0.8437	0.5900	0.1687	0.1855
Bottom-3	2.0285	2.1695	2.8519	2.9908	3.6777	3.6897	3.8501

depth levels of sampling. The original concentration of ibuprofen in every suspension was 2g/100 mL. Good suspension should have a uniformity of content i.e.; the concentration should be the same at any depth level of the container. Content deviation was calculated as a deviation of concentrations obtained from different depth levels. Low value of content deviation basically implies that the suspension has a high content uniformity of drug dispersion during storage. In this experiment, only 14 suspensions those exhibited homogeneity were subjected to uniformity of drug dispersion during storage evaluation. The reamining 13 suspensions that showed visible separation or sedimentation were not included.

The content deviation graphs of 14 tested suspensions containing different types and concentrations of suspending agent are shown in Figures 75-80. Figure 75 represents the content deviation of ibuprofen suspension containing 1, 2, and 3% XG as suspending agents. All three suspensions showed good uniformity in the first two weeks, with the deviation of content only 0.01-0.04 g/100 mL (0.5-2%). After four weeks, suspension that contained 1% XG showed rapid increase in content deviation with the value of 0.13 g/100 mL at the end of week 12. The content deviation of suspensions that contained 2% and 3% XG increased slowly after four weeks and the values at week 12 were 0.06 and 0.04 g/100 mL, respectively.

Figure 76 displayed the content deviation of ibuprofen suspension containing 3% TG. The content deviation was 0.01 g/100 mL at week 0 and increased to 0.04 g/100 mL at the end of the evaluation. Figure 77 showed that the content deviation of

Figure 75 Comparative Deviation of Ibuprofen Content of Suspension Containing 1, 2, and 3% Xanthan Gum as Suspending Agent

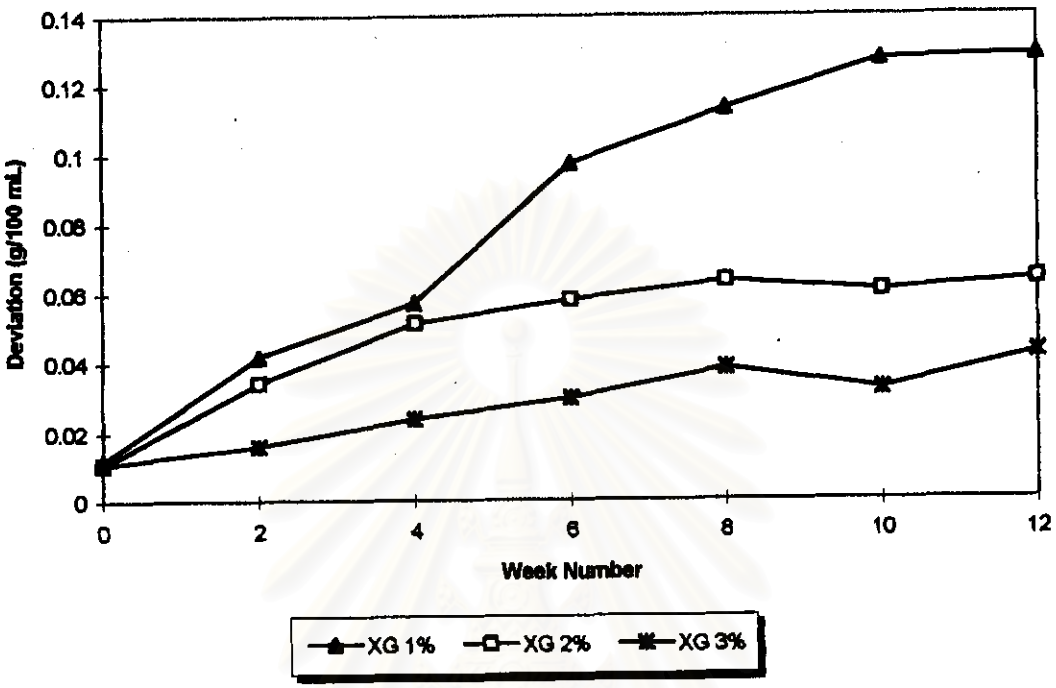


Figure 76 Comparative Deviation of Ibuprofen Content of Suspension Containing 3% Tragacanth as Suspending Agent

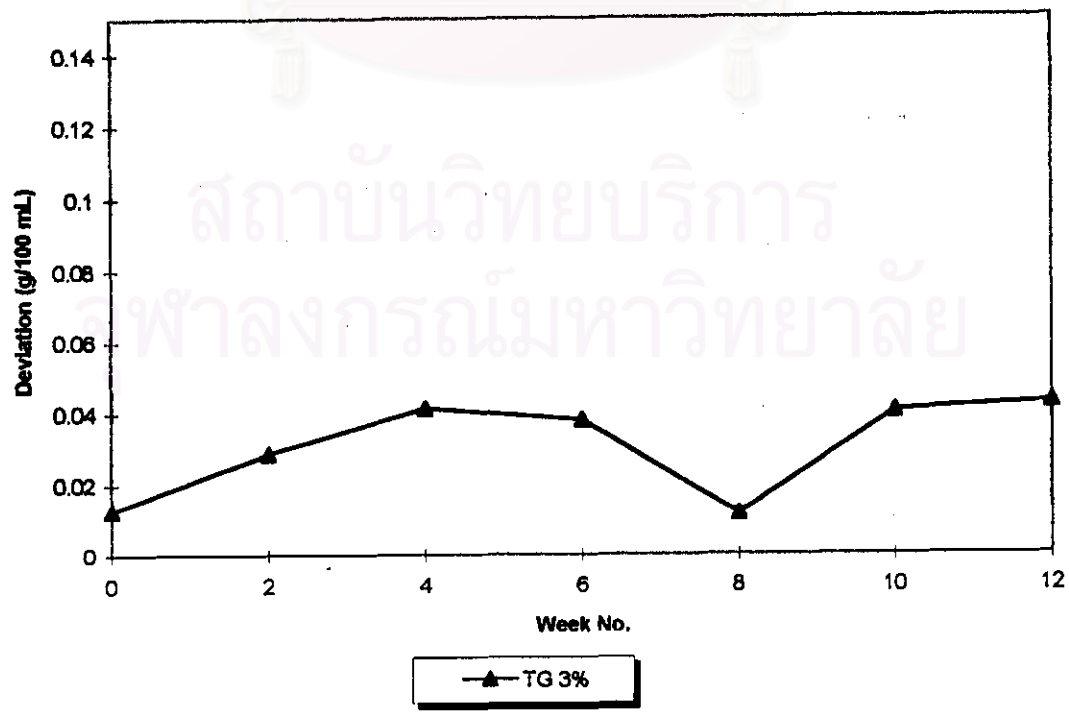


Figure 77 Comparative Deviation of Ibuprofen Content of Suspension Containing 1 and 2% SCMC as Suspending Agent

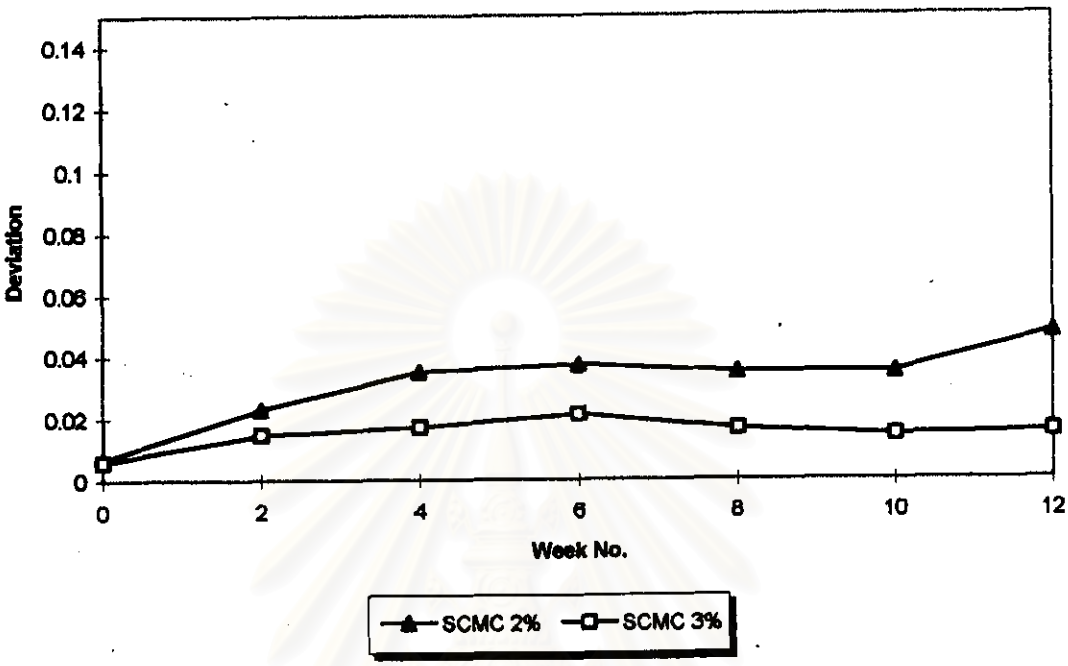
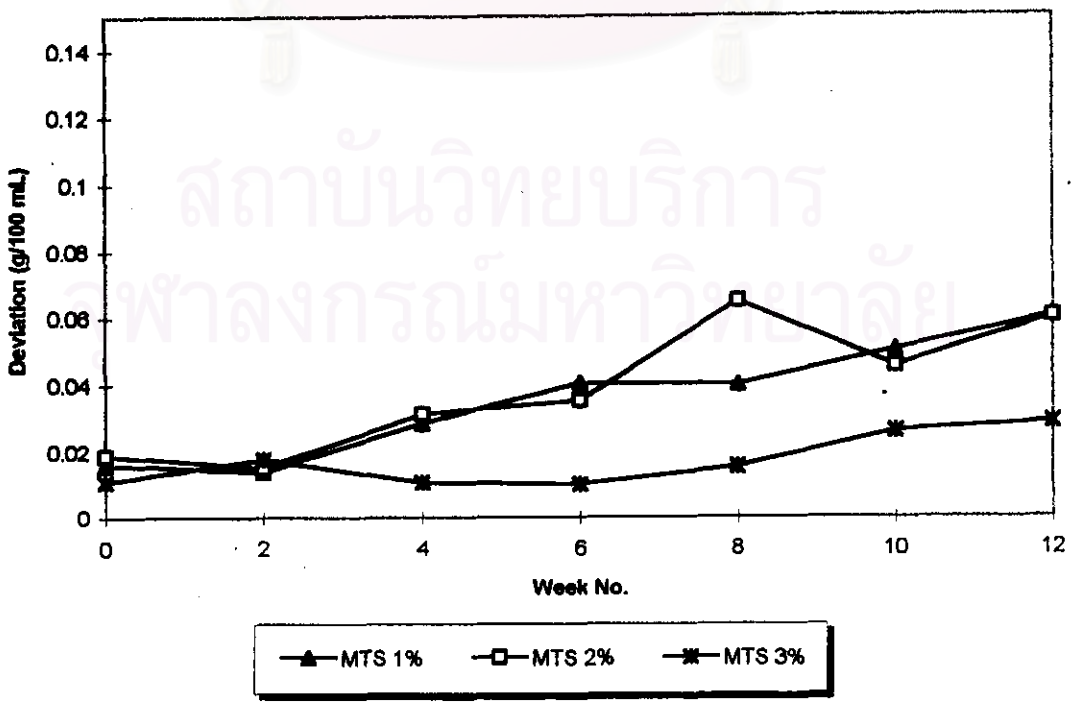


Figure 78 Comparative Deviation of Ibuprofen Content of Suspension Containing 1, 2 and 3% MTS as Suspending Agent



ibuprofen suspensions containing 2% and 3% SCMC. Both suspensions showed good uniformity over evaluation period and had the final value of 0.04 and 0.02 g/100 mL, respectively.

Figure 78 represented the content deviation of ibuprofen suspensions containing 1,2, and 3% of MTS. Suspension that contained 3% MTS showed the most promising uniformity with only small increase in content deviation over the period of 12 weeks. The other two MTS containing suspensions showed a slow increase in content deviation after two weeks until the end of the evaluation. The final values of content deviation for 1,2, and 3% MTS containing suspensions were 0.06, 0.06, and 0.03 g/100 mL, respectively.

Figure 79 displays the content deviation of ibuprofen suspensions containing MRS as suspending agent. Suspension that contained 1% MRS showed a steady increase in content deviation after week 0 and finished with the value of 0.05 g/100 mL, the highest among all three MRS containing suspensions. Suspension that contained 3% MRS showed only small increase in content deviation over the evaluation period and has the final value of 0.03 g/100 mL. The 2% MRS containing suspension had the final value of 0.04 g/100 mL.

Figure 80 represents the content deviation of ibuprofen suspensions containing 2% and 3% MGS as suspending agent. Both suspensions expressed a similar pattern of increase in content deviation. The deviation started at week 0 and rapidly increased as

Figure 79 Comparative Deviation of Ibuprofen Content of Suspension Containing 1, 2 and 3% MRS as Suspending Agent

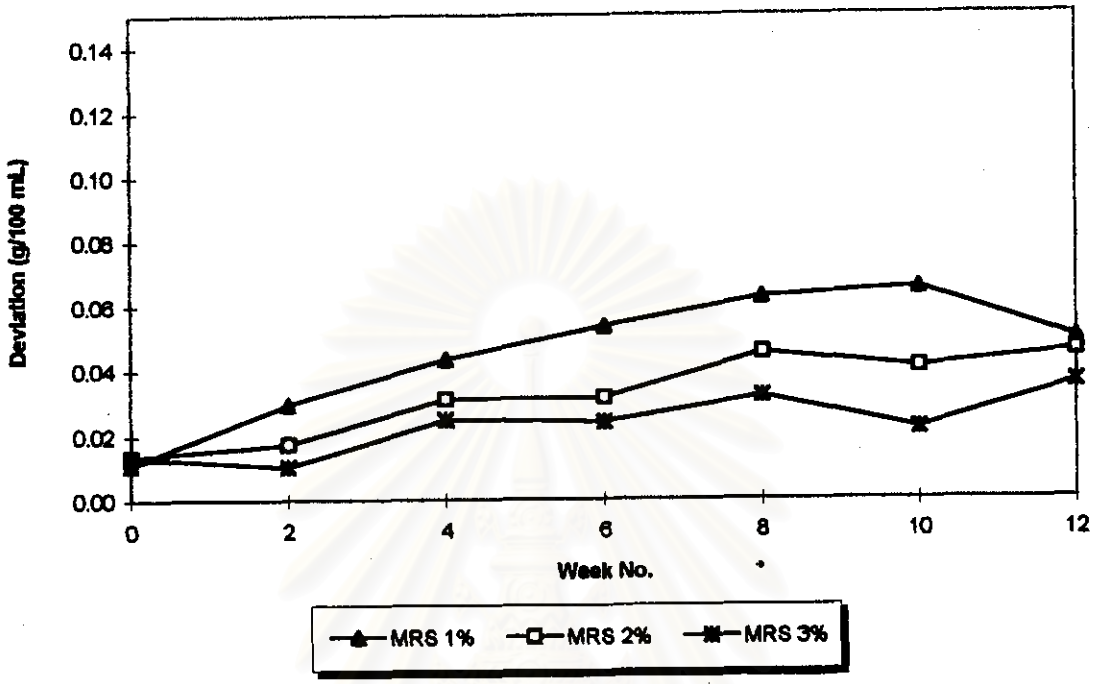
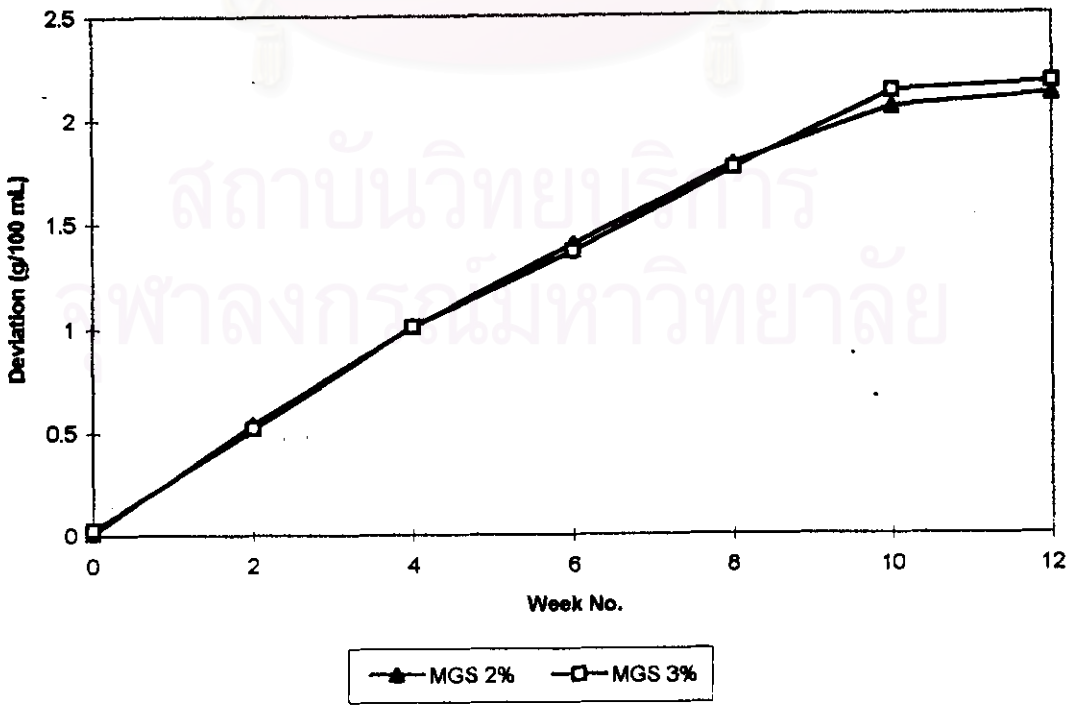


Figure 80 Comparative Deviation of Ibuprofen Content of Suspension Containing 2 and 3% MGS as Suspending Agent



time proceeded. The value of content deviation of both suspensions approached 2 g/100 mL at week 10 and remained steady until the final week.

The statistical differences of ibuprofen content deviation among different weeks of each suspension are presented in Table 57-84 (Appendix II). The rank order of the deviations of ibuprofen content in suspensions was; SCMC 3% < MTS 3% < MRS 3% < XG 3% < SCMC 2% < MRS 2% < TG 2% < MTS 1% < MTS 2% < MRS 1%< XG 2% < XG 1% < MGS 2% < MGS 3%. Therefore, suspension containing 3% SCMC provided the best uniformity of ibuprofen content during storage while suspension containing 3% MGS possessed the worst uniformity among all evaluated suspensions.

Overall statistical analysis for the differences of ibuprofen content deviation among suspensions containing different suspending agents are presented in Table 85-86 (Appendix II). The result indicated that no significant differences in uniformity of drug dispersion during storage was observed among suspensions containing different suspending agents except for MGS 2% and MGS 3% which were different from the others.

The statistical analysis was performed in both within a suspension and among suspensions. The analysis within a suspension provided the information on whether the content deviation of suspension among different weeks were different from one another. From this information, the rank of content deviation was obtained. In order to indicate whether one suspension is better than another, another analysis was

performed. This second analysis indicated whether the content deviation of one suspension was different from another.

It should be noted that the suspensions that contained 1% Xg as suspending agent possessed inferior content uniformity when compared to 1% MTS or MRS containing suspensions. This is contrast with the sedimentation volume study which indicated that XG was the best suspending agent among all employed in this study. However, the statistical analysis has suggested that no difference in content deviationwere found among suspensions except those contained 2% and 3% MGS, the rank can be ignored.

Comparison of General Characteristics of Ibuprofen Suspensions Containing 1% Suspending Agents

The comparison of prepared suspensions containing 1% suspending agents, except that contained MGS, are shown in Figure 81. The 1% concentration was selected in this comparison according to the results of this study that showed that 1% concentration of modified starches was high enough to exhibit the preferred suspending property. At this concentration. MTS and MRS containing suspensions clearly exhibited better appearance, homogeneity, and uniformity of drug dispersion during storage, compared to AC, AV, TG, SA, and SCMC. They have high sedimentation volume and can easily be dispersed. The viscosity of the two suspensions was moderate but high enough to support the contents and not too high that would interfere with pouring. The redispersal produces a dose with high

Figure 81 Ibuprofen Suspension (2g/100 mL) Prepared Using 1% Suspending Agents

uniformity. Neither chemical nor physical instability is observed. The suspensions have an agreeable odor, color, and taste. MTS containing suspension was a little more viscous than MRS containing suspension. From these general appearances, MTS and MRS containing suspensions are obviously superior to those contained other suspending agent.

Application of Modified Starches in Manufacturing of Suspension Products

The interest in the use of starch in pharmaceutical product has shifted the focus from native starches to a variety of modified starches. The advantage of modified starches is their improvement in flowability, viscosity, and swelling ability while maintaining the inert property. The use of modified starh has already been attemptd as tablet disintegrant (Thavisak Theruya, 1995) and as tablet binder (Tasana Pitaksuteepong, 1995) with satisfactory outcomes. Employing ibuprofen as a model drug in suspension products, the viscosity and the redispersibility of modified starches, especially MRS and MTS suggested that they would be novel candidates for suspensing agent.

The use of modified starches in suspension could decrease the overall cost of suspension products due to the abundance of starch in the country. The cost of modified starch production is lower comapred to other suspending agents. The production procedures are readily available and the improvement to industrial scale could be done to decrease the cost.