

CHAPTER III

RESULTS AND DISCUSSION

1. Preparation of Modified Sodium Carboxymethylcellulose

The procedure of modification of sodium carboxymethylcellulose was similar to the cross-linking reaction of starch from Kerr et al.'s method (1957). The phosphorylation of starch more efficiently at a high pH, preferably at 11.0 or above although a pH of about 9.0 was satisfactory. In general temperatures between 40°C and 50°C were satisfactory. A practical operating range of metaphosphate was about 0.01 to about 3 percent. Although amounts higher than about 0.6 percent were not detrimental for these conditions, such amounts serve no useful purpose. It had been found that the concentration of sodium added as a sodium salt had an effect on the degree of phosphorylation, the higher the concentration (within practical limits) the higher the degree of phosphorylation. A total sodium ion concentration of about 0.4 mole per litre gave satisfactory results.

In this study, 5 g of sodium hydroxide gave the pH of sodium carboxymethylcellulose dispersion about 12. The temperature was set at 50 ±1°C. The amount of sodium trimetaphosphate was 3 percent, based on the dry weight of the sodium carboxymethylcellulose. And 25.44 g of sodium carbonate anhydrous was added, which gave total sodium ion concentration of 0.4194 mole per litre. The percent yield of product was in the range of 104.38-110.62.

The reason for selection sodium trimetaphosphate as a cross-linking agent was that it has been approved for use in food by The Food Additive Regulations (Hamilton and Paschall, 1967).

1.1 Effect of Ratio of Methanol to Water on Crosslinking Reaction between Sodium Carboxymethylcellulose and Sodium Trimetaphosphate

NaCMC₂ was used to study the effect of ratio of methanol to water on cross-linking reaction between sodium carboxymethylcellulose and sodium trimetaphosphate. The result of sodium carboxymethylcellulose cross-linked with sodium trimetaphosphate with the varying in the ratio of MeOH to H₂O are shown in Table 6. It was found that too low ratio of MeOH to H₂O caused the flake-like particles. The explanation of this appearance was the solubility of sodium carboxymethylcellulose in water. The higher amount of water, the higher sodium carboxymethylcellulose dissolved. Consequently, the gel formation around particles occurred. When the product dried, the flaked-like particles were obtained.

Table 6 The appearance of sodium carboxymethylcellulose cross-linked with sodium trimetaphosphate with the varying in the ratio of methanol to water

MeOH : H ₂ O	Appearance of product
50 : 50	flake-like particles
60 : 40	flake-like particles
70 : 30	white, odorless powders
80 : 20	dry, char particles

Conversely, if the ratio of MeOH to H₂O was too high the cross-linking reaction could not go on. It can be explained that methanol gradually evaporated while the cross-linking reaction taking place. Finally, the reduction of solvent caused sodium carboxymethylcellulose dispersion dried and charred at the bottom of the reaction container. In this study, it was found that the optimal ratio of methanol to water that gave the satisfactory cross-

linked sodium carboxymethylcellulose was 70 : 30. This product occurred white and odorless powders.

1.2 Effect of Time on Crosslinking Reaction between Sodium Carboxymethylcellulose and Sodium Trimetaphosphate

The cross-linking reaction of NaCMC₂ and sodium trimetaphosphate in 70% MeOH : 30% H₂O was selected to study the effect of time on cross-linking reaction. In varying the time of cross-linking reaction, the results are shown in Table 7. The appearance of modified sodium carboxymethylcellulose at various cross-linking time were similar. Thus, the phosphate content and viscosity of modified sodium carboxymethylcellulose were considered so that the optimal cross-linking time would be selected for the further investigation. The phosphate content of modified sodium carboxymethylcellulose which cross-linked for 3, 6, 12 and 24 hours was 4.38, 4.34, 4.36 and 4.37%, respectively. No statistical difference ($p < 0.05$) was found among these modified sodium carboxymethylcellulose (Table 35 and 36 in Appendix III). From Table 7, it can be seen that the cross-linking time affected the viscosity of modified sodium carboxymethylcellulose. When the cross-linking time increased from 3 to 6 hours, the viscosity of modified sodium carboxymethylcellulose was decreased from 174.33 to 160.00 cps and that was increased to 177.33 and 186.67 cps at the cross-linking time of 12 and 24 hours, respectively. The statistical differences ($p < 0.05$) are shown in Table 37 and 38 (Appendix III). It showed that the significantly difference of viscosity was observed in modified sodium carboxymethylcellulose cross-linked at 6 and 24 hours. The shortest cross-linking time (3 hours) would be chosen for the further investigation because the modified sodium carboxymethylcellulose obtained had the highest phosphate content and the viscosity was not too high.

Table 7 Phosphate content and viscosity of modified sodium carboxymethylcellulose at various cross-linking time

Cross-linking time (hour)	Appearance of product	Phosphate* (%) ± SD	Viscosity* (cps) ± SD
3	white, odorless powders	4.38 ± 0.04	174.33 ± 13.58
6	white, odorless powders	4.34 ± 0.02	160.00 ± 8.72
12	white, odorless powders	4.36 ± 0.05	177.33 ± 6.11
24	white, odorless powders	4.37 ± 0.04	186.67 ± 5.86

* The mean of three determinations

1.3 Effect of Viscosity of Sodium Carboxymethylcellulose on Crosslinking Reaction between Sodium Carboxymethylcellulose and Sodium Trimetaphosphate

The sodium carboxymethylcellulose with different viscosity grade were cross-linked with sodium trimetaphosphate in 70% MeOH : 30% H₂O for 3 hours. The results are shown in Table 8. In general, the appearance of various modified sodium carboxymethylcellulose obtained were similar. Therefore, the chemical and physical properties of these materials would be further determined.

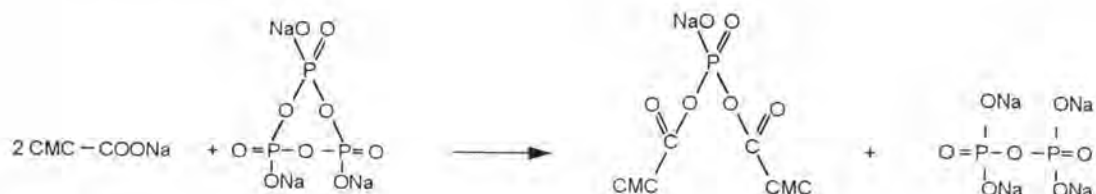
Table 8 The appearance of sodium carboxymethylcellulose cross-linked with sodium trimetaphosphate with the varying in the viscosity of sodium carboxymethylcellulose

Material	Appearance of product
NaCMC ₁	white, odorless powders
NaCMC ₂	white, odorless powders
NaCMC ₃	white, odorless powders
NaCMC ₄	white, odorless powders

2. Detection Crosslinking Reaction in Modified Sodium Carboxymethylcellulose

The degree of cross-linking of modified sodium carboxymethylcellulose was determined similar to that of starch. Usually, the degree of cross-linking for modified starch was not determined by the extent of cross-linking but prefer to examined the physical properties such as viscosity, swelling power, solubility pattern and resistance to the shear (Chalmers, 1968).

The cross-linking reaction of modified sodium carboxymethylcellulose may be represented as:



2.1 Percent Phosphate

The percentage of phosphorus and phosphate in modified sodium carboxymethylcellulose in comparison to sodium carboxymethylcellulose and physical mixture of sodium carboxymethylcellulose and sodium trimetaphosphate are shown in Table 9.

For modified sodium carboxymethylcellulose, they were ranked as in the following : $M_1 > M_3 > M_2 > M_4$. The statistical differences ($p < 0.05$) are shown in Table 39 and 40 (Appendix III). It showed that no significantly difference in the group of M_2 and M_3 . Phosphorus and phosphate content were not found in sodium carboxymethylcellulose and Ac-di-sol[®].

Table 9 Phosphorus and phosphate content in sodium carboxymethylcellulose and modified sodium carboxymethylcellulose

Material	Phosphorus* (%) \pm SD	Phosphate* (%) \pm SD
M ₁	1.55 \pm 0.01	4.76 \pm 0.04
M ₂	1.43 \pm 0.01	4.38 \pm 0.04
M ₃	1.44 \pm 0.02	4.41 \pm 0.05
M ₄	1.40 \pm 0.01	4.28 \pm 0.02
NaCMC ₃	0.00 \pm 0.00	0.00 \pm 0.01
NaCMC ₃ + Na ₃ P ₃ O ₉ **	1.21 \pm 0.01	3.71 \pm 0.02
Ac-di-sol [®]	0.00 \pm 0.00	0.00 \pm 0.00

* The mean of three determinations

** The physical mixture of NaCMC₃ and sodium trimetaphosphate

2.2 IR Spectrophotometry

The infrared spectra of sodium carboxymethylcellulose of various viscosity grades, modified sodium carboxymethylcellulose and sodium trimetaphosphate are shown in Figure 2-4. The infrared spectra of carboxylic acid salt showed strong carbonyl bands at 1610 to 1550 cm^{-1} and near 1400 cm^{-1} (Pasto, Johnson and Miller, 1992). For modified sodium carboxymethylcellulose, the absorption peak at 1050 to 970 cm^{-1} represented P-O-C (aliphatic).

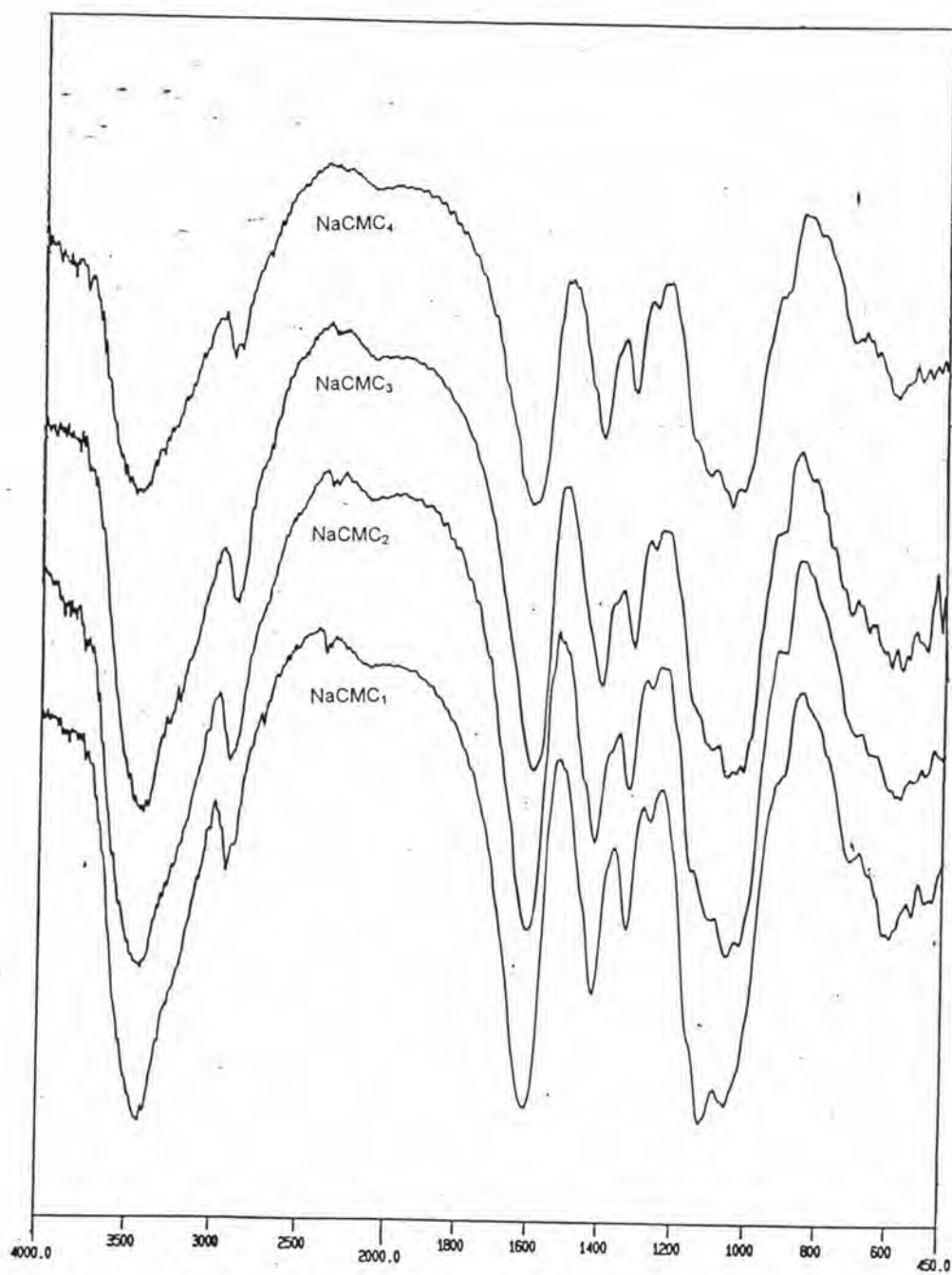


Figure 2 IR spectra of sodium carboxymethylcellulose of various viscosity grades

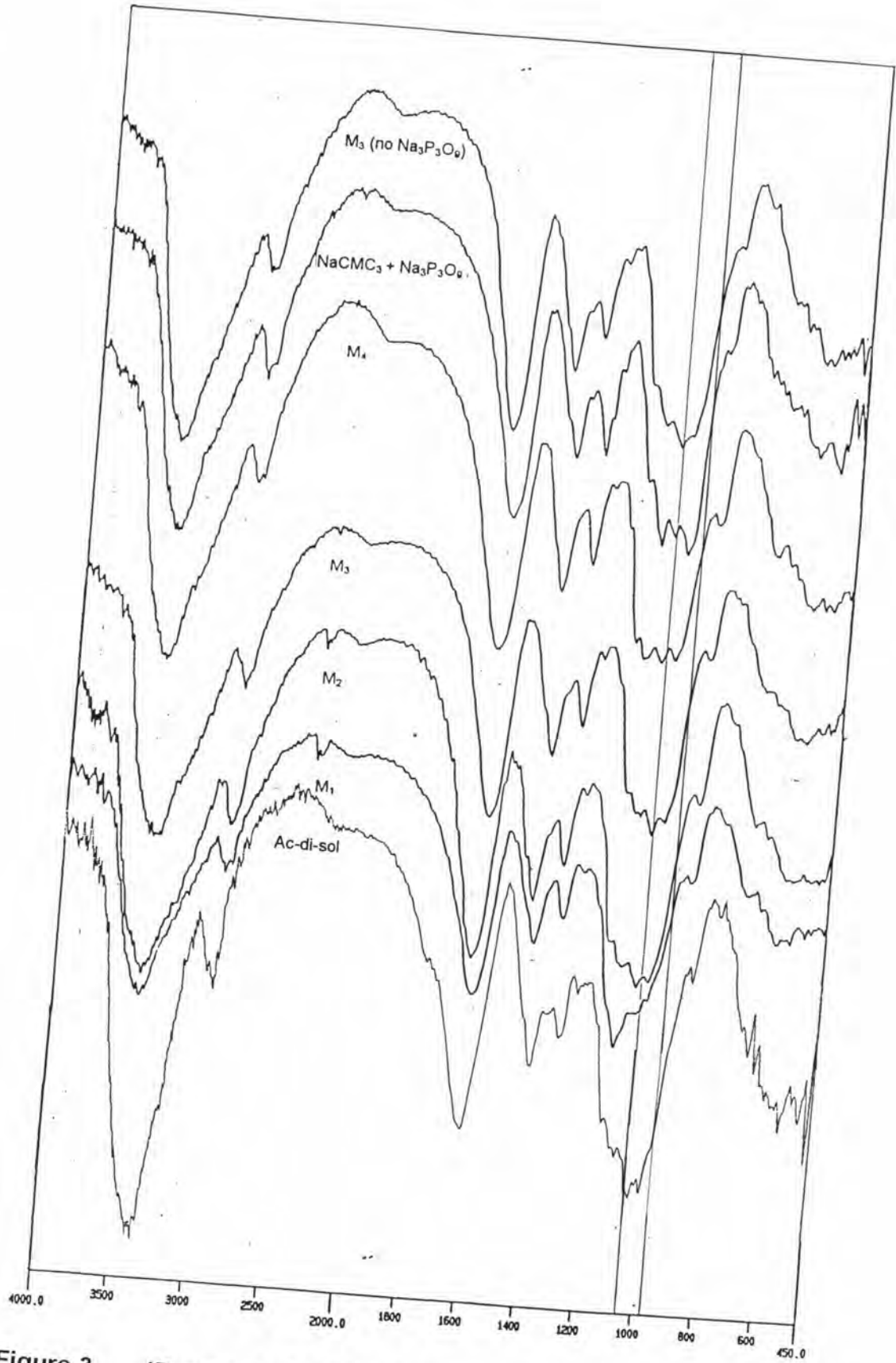


Figure 3 IR spectra of modified sodium carboxymethylcellulose

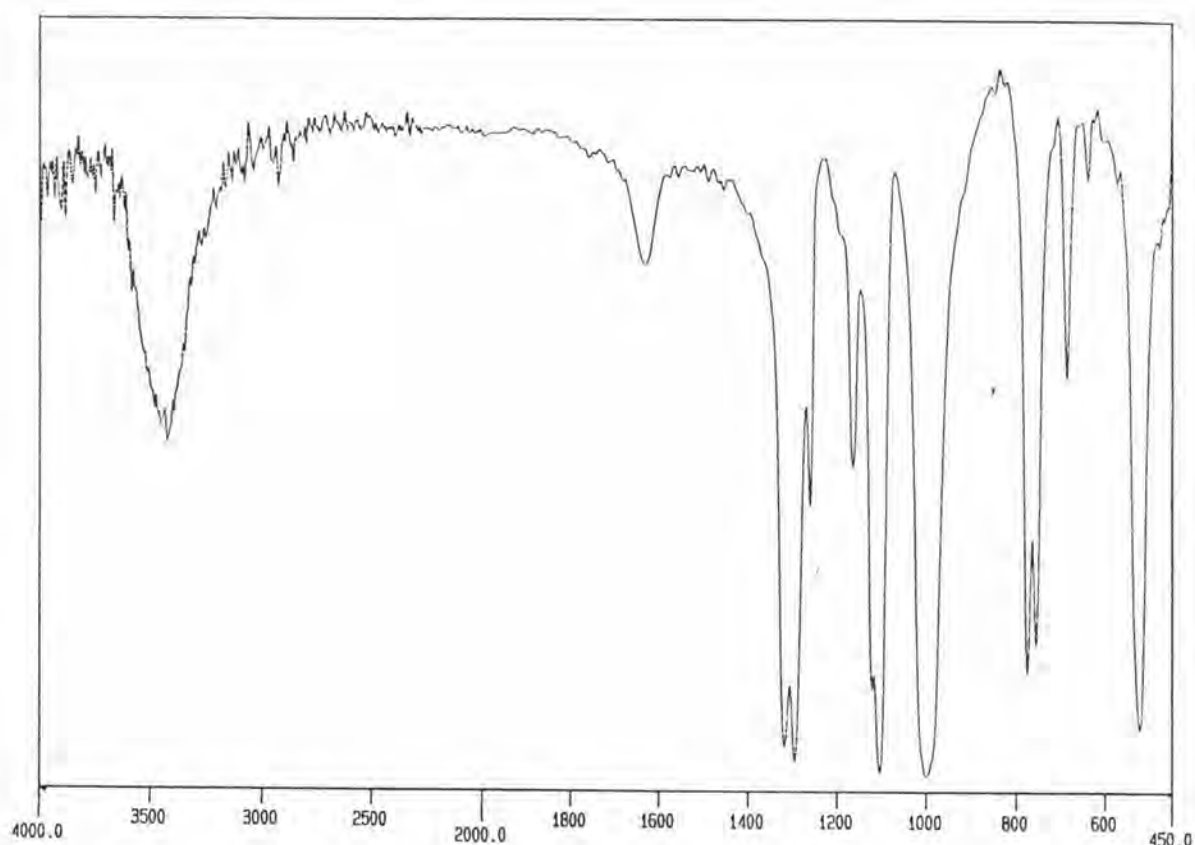


Figure 4 IR spectra of sodium trimetaphosphate

The relative quantitative evaluation of modified sodium carboxymethylcellulose was performed by using infrared spectrophotometry. The peak height ratios were used to determine the relative quantitative of phosphorus cross-linked. Using the absorption peak at 2000 cm^{-1} as a reference, measured the peak height at about 1020 cm^{-1} . The peak height ratio of phosphorus cross-linked of $M_1 : M_2 : M_3 : M_4$ was $0 : 1 : 1.004 : 0.986$ (The data are shown in Table 55, Appendix IV). This could be concluded that the phosphorus cross-linked was taken place, which was characterized by a specific absorption band at about 1020 cm^{-1} . This result correlated with the data of percent phosphate which determined by UV-visible spectrophotometry except M_1 . The absorption peak of M_1 was not found but percent phosphate of M_1 was 4.76% (from the previous section). From Figure 3, it can be seen that the absorption peak about 1020 cm^{-1} of sodium carboxymethylcellulose which treated with the same condition of cross-linking reaction but no added

sodium trimetaphosphate (M_3 (no $Na_3P_3O_9$)) was not found, that was no absorption peak of P-O-C (aliphatic) of M_3 (no $Na_3P_3O_9$). For Ac-di-sol[®], it showed the absorption peak at about 1020 cm^{-1} but the determination of phosphorus and phosphate content by UV-visible spectrophotometry were not found. Therefore, it can be concluded that the cross-linking agent for Ac-di-sol[®] was not the same as the cross-linking agent used in this study, sodium trimetaphosphate.

Hullinger (1967) claimed that direct analysis of the extent of cross-linking is difficult because of the very low degree of substitution in most cross-linked starches. Radioactive tracer techniques should prove useful, but none has been reported to date.

2.3 Differential Scanning Calorimetry

The DSC thermograms of sodium trimetaphosphate, sodium carboxymethylcellulose and modified sodium carboxymethylcellulose are revealed in Figure 5. And the DSC peak temperature of these materials are shown in Table 10. The DSC thermogram of sodium trimetaphosphate did not showed endothermic peak. Most grades of cellulose without prior treatment display a broad endotherm in the range $75\text{-}120^\circ\text{C}$ which corresponds to loss of unbound water (Ford and Timmins, 1989). The endothermic peak of modified sodium carboxymethylcellulose, the physical mixture of $NaCMC_3$ and sodium trimetaphosphate and $NaCMC_3$ which treated with the same condition of cross-linking reaction but no added sodium trimetaphosphate differed from that of sodium carboxymethylcellulose. These results confirmed that the physical property of all modified sodium carboxymethylcellulose product differed from sodium carboxymethylcellulose used as the starting material, which may be due to the condition of cross-linking reaction or cross-linking agent.

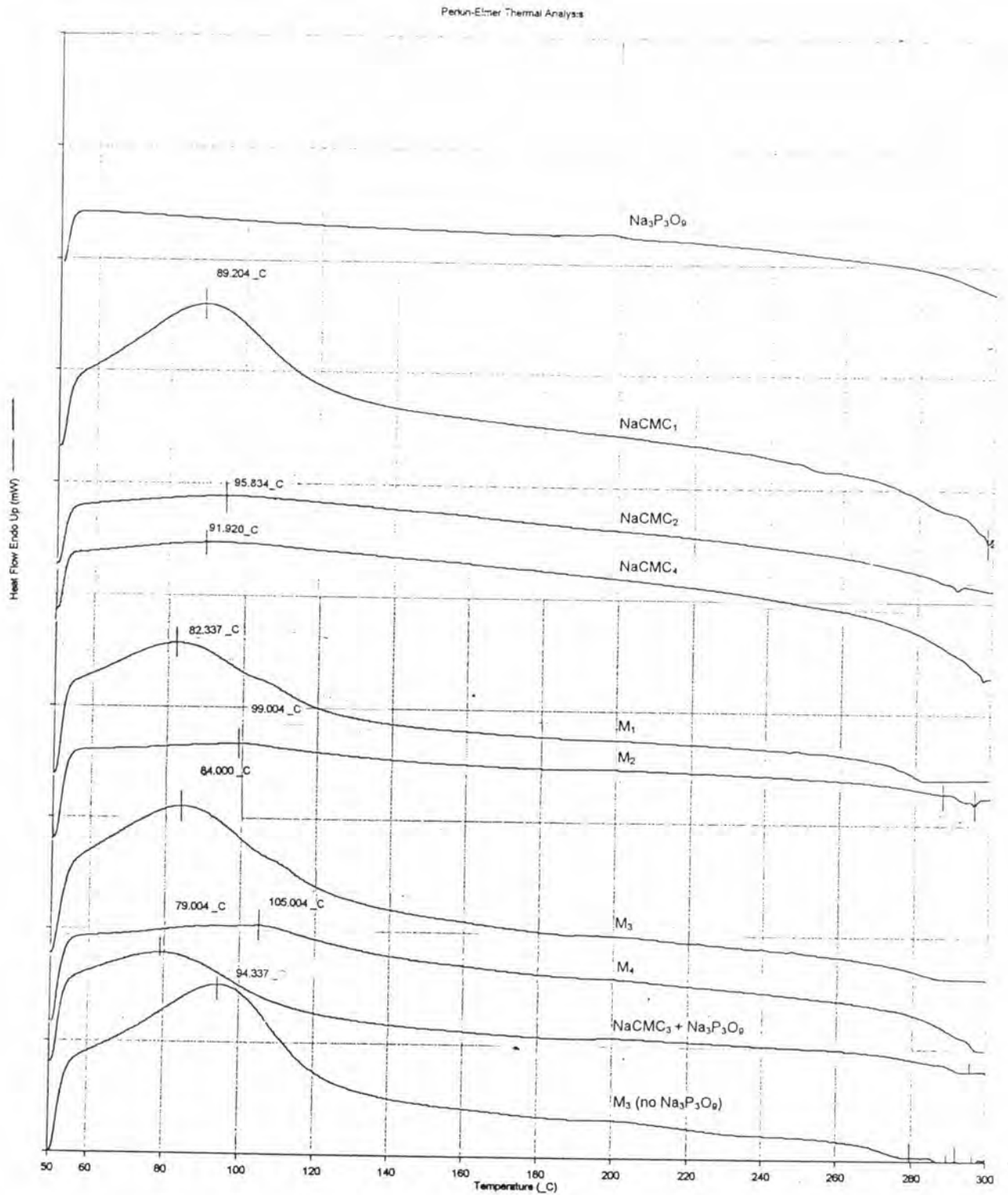


Figure 5 DSC thermograms of sodium trimetaphosphate, sodium carboxymethylcellulose and modified sodium carboxymethylcellulose

Table 10 DSC peak temperature of sodium trimetaphosphate, sodium carboxymethylcellulose and modified sodium carboxymethylcellulose

Material	Temperature of endothermic peak (°C)
Na ₃ P ₃ O ₉	-
NaCMC ₁	89.20
NaCMC ₂	95.83
NaCMC ₄	91.92
M ₁	82.34
M ₂	99.00
M ₃	84.00
M ₄	105.00
NaCMC ₃ + Na ₃ P ₃ O ₉ *	79.00
M ₃ (no Na ₃ P ₃ O ₉)**	94.34

* The physical mixture of NaCMC₃ and sodium trimetaphosphate

** NaCMC₃ which treated with the same condition of cross-linking reaction but no added sodium trimetaphosphate

2.4 Viscosity

The results of viscosity are shown in Table 11. They could be ranked as follows: NaCMC₁ < M₁ < M₂ < M₃ < M₄ < M₃ (no Na₃P₃O₉) < NaCMC₂ < NaCMC₃ < NaCMC₂ + Na₃P₃O₉ < NaCMC₄. The statistical differences ($p < 0.05$) are shown in Table 41 and 42 (Appendix III). In comparison to sodium carboxymethylcellulose used as starting materials, it could be noticed that the viscosity of sodium carboxymethylcellulose cross-linked with sodium trimetaphosphate was significantly decreased except that of M₁ was increased. This may be due to the viscosity of NaCMC₁ and M₁ were very low therefore the variation of determination would be occurred. However, the viscosity of NaCMC₁ and M₁ were not significantly difference.

Table 11 Viscosity of sodium carboxymethylcellulose and modified sodium carboxymethylcellulose

Material	Viscosity* (cps) \pm SD
NaCMC ₁	29.10 \pm 1.00
M ₁	41.80 \pm 2.76
NaCMC ₂	354.67 \pm 26.10
M ₂	174.33 \pm 13.58
NaCMC ₃	433.67 \pm 10.79
M ₃	219.00 \pm 13.23
NaCMC ₄	910.33 \pm 80.05
M ₄	237.33 \pm 28.57
NaCMC ₃ + Na ₃ P ₃ O ₉ **	609.33 \pm 7.50
M ₃ (no Na ₃ P ₃ O ₉)***	344.33 \pm 14.43

* The mean of three determinations

** The physical mixture of NaCMC₃ and sodium trimetaphosphate

*** NaCMC₃ which treated with the same condition of cross-linking reaction but no added sodium trimetaphosphate

For NaCMC₃ which treated with the same condition of cross-linking reaction except no added sodium trimetaphosphate (M₃ (no Na₃P₃O₉)), the viscosity was 344.33 cps which significantly less than the starting material (433.67 cps) and significantly more than M₃ (219.00 cps). And the physical mixture of NaCMC₃ and sodium trimetaphosphate had significantly higher viscosity than NaCMC₃ and M₃ that was 609.33 cps ($p < 0.05$). The explanation for the difference of viscosity of physical mixture of NaCMC₃ and sodium trimetaphosphate and NaCMC₃ was the interaction between the charge of sodium carboxymethylcellulose and sodium trimetaphosphate.

These results showed that the cross-linking reaction could be decreased the viscosity of sodium carboxymethylcellulose, that was the desired property of a good disintegrant.

3. Physical Properties of Modified Sodium Carboxymethylcellulose

3.1 Powder Morphology

The photomicrographs of various sodium carboxymethylcellulose and modified sodium carboxymethylcellulose in different magnification are shown in Figure 6-13. The general size and shape of individual particle could be clearly observed. It was seen as irregular shape particles with varying in size at low magnification ($\times 50$). The higher magnification ($\times 200$) revealed that they were the agglomeration of fiber-like shape particles. For NaCMC₁, it was different from others sodium carboxymethylcellulose used in this study that the agglomeration of NaCMC₁ particles had somewhat round and surface topography was rough whereas the others sodium carboxymethylcellulose had also individual fiber-like shape particle. From the photomicrographs they could be noticed that NaCMC₂ and NaCMC₃ had longer individual fiber-like shape particle than NaCMC₄. When the various sodium carboxymethylcellulose were modified by cross-linked with sodium trimetaphosphate in the optimal condition, the morphology of modified sodium carboxymethylcellulose obtained were similar to the starting material, sodium carboxymethylcellulose.

3.2 Size Distribution and Specific Surface Area

The particle size distribution of various sodium carboxymethylcellulose and modified sodium carboxymethylcellulose were analyzed by laser diffraction particle size analyzer. The data for average particle size and specific surface area of sodium carboxymethylcellulose and modified sodium carboxymethylcellulose are summerized in Table 12.

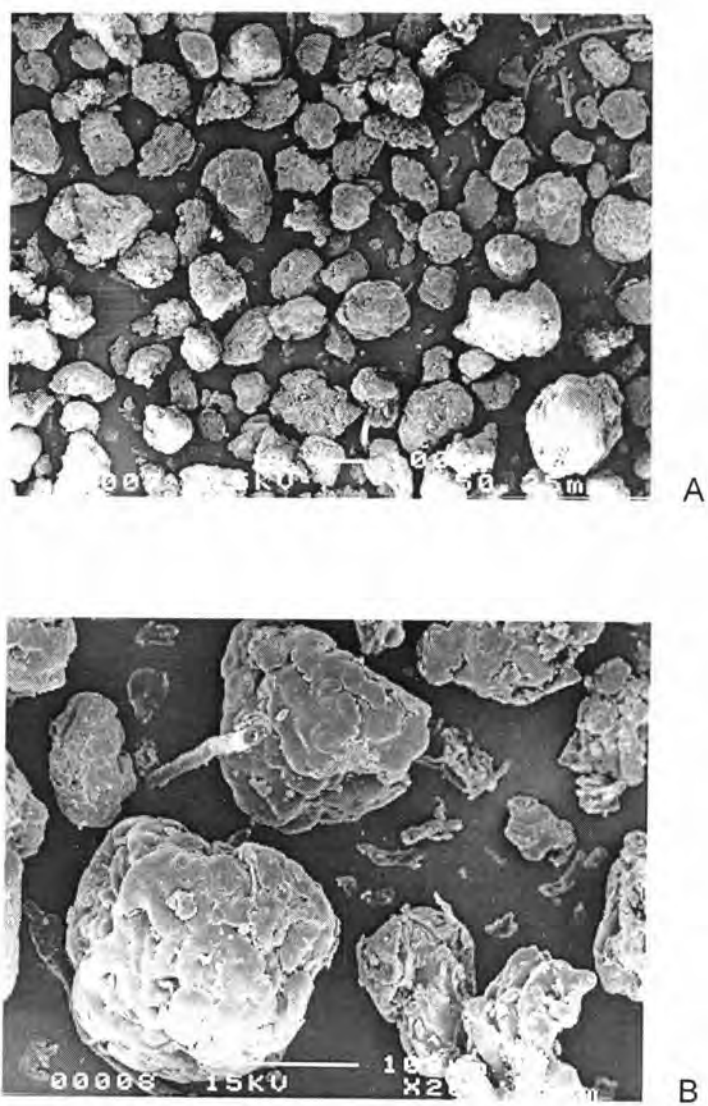


Figure 6 Photomicrographs of NaCMC₁ (A ×50 , B ×200)

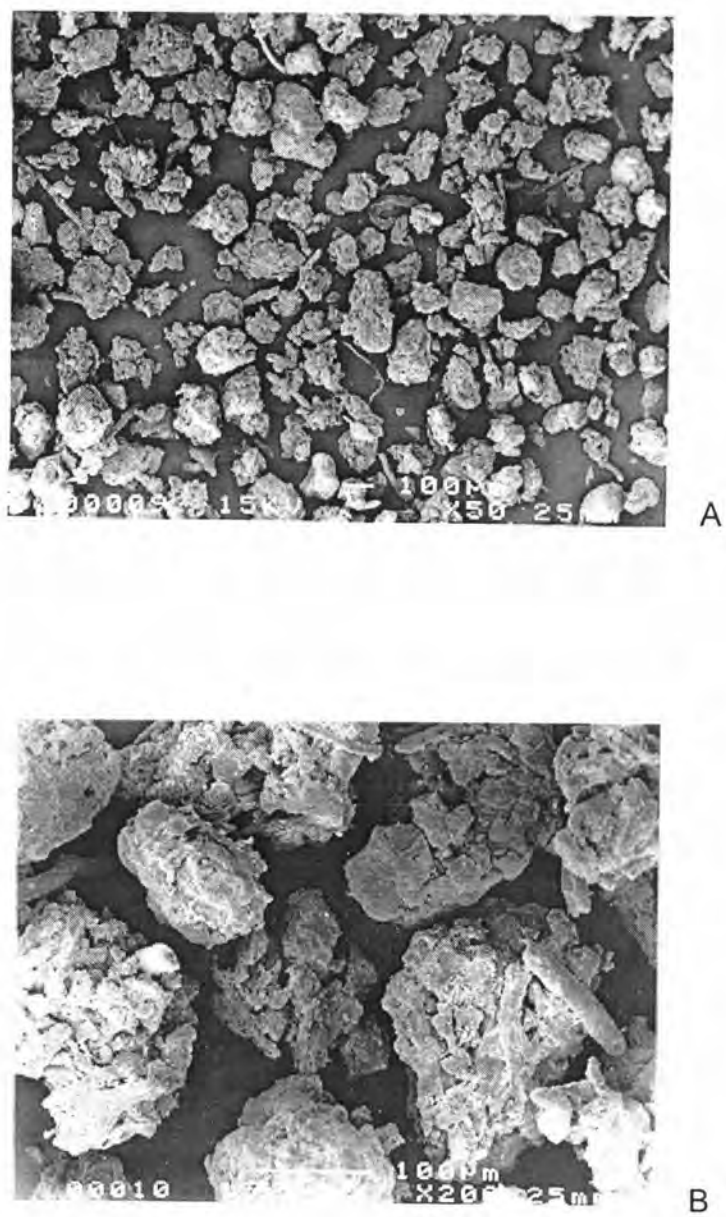
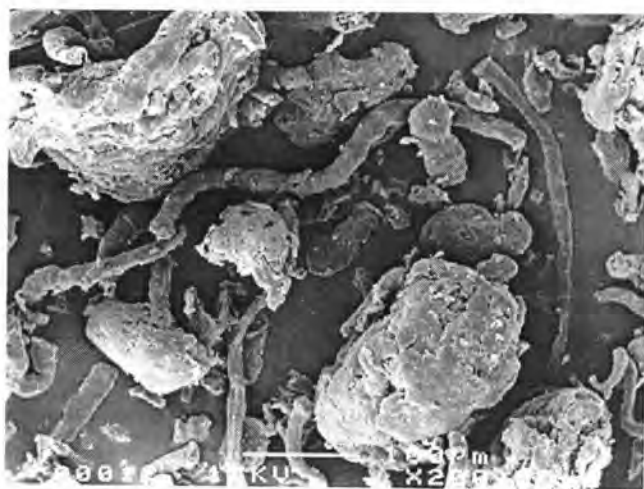


Figure 7 Photomicrographs of M_1 (A $\times 50$, B $\times 200$)

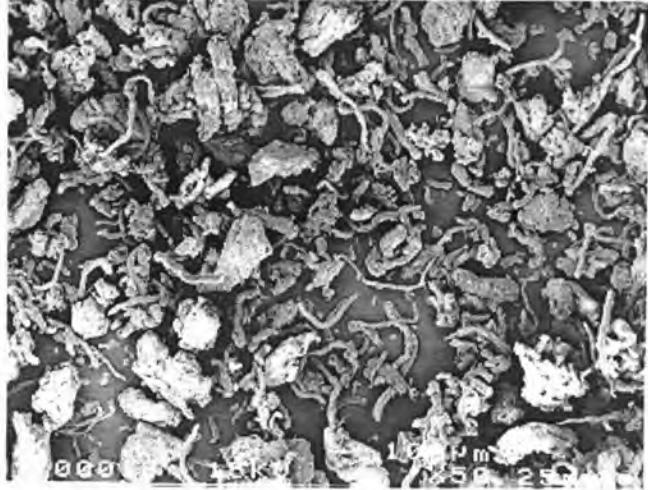


A

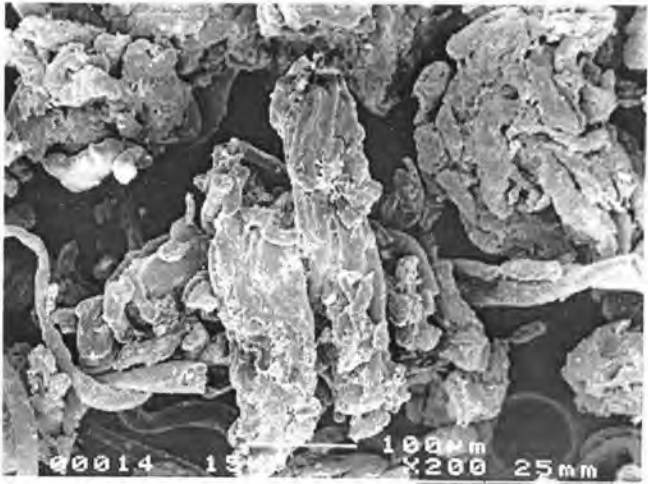


B

Figure 8 Photomicrographs of NaCMC₂ (A ×50 , B ×200)



A



B

Figure 9 Photomicrographs of M_2 (A $\times 50$, B $\times 200$)

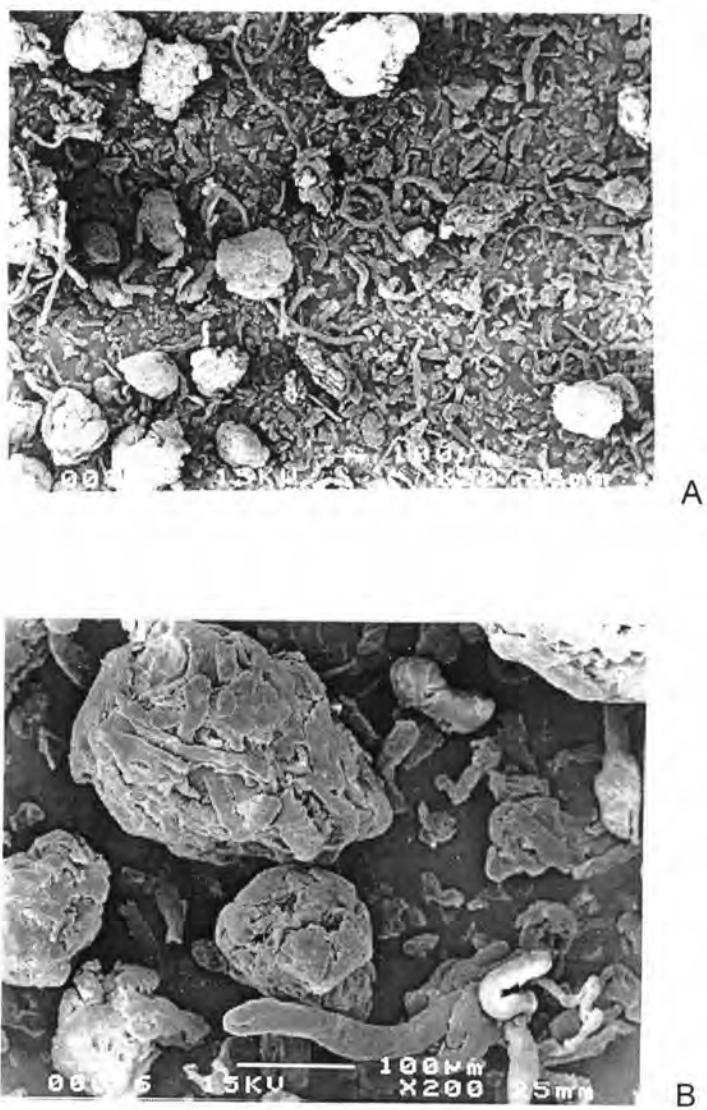
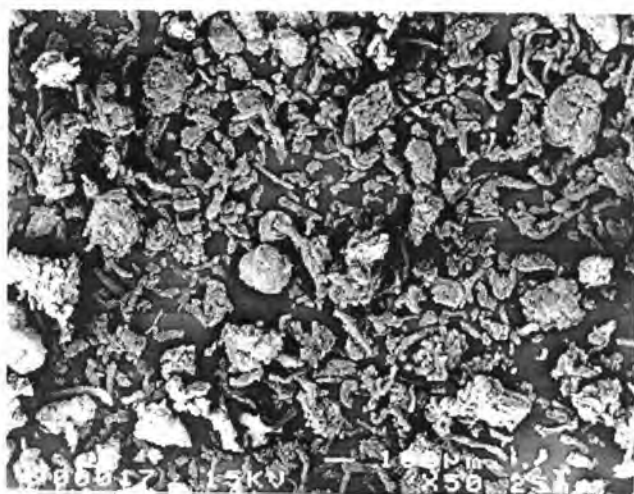
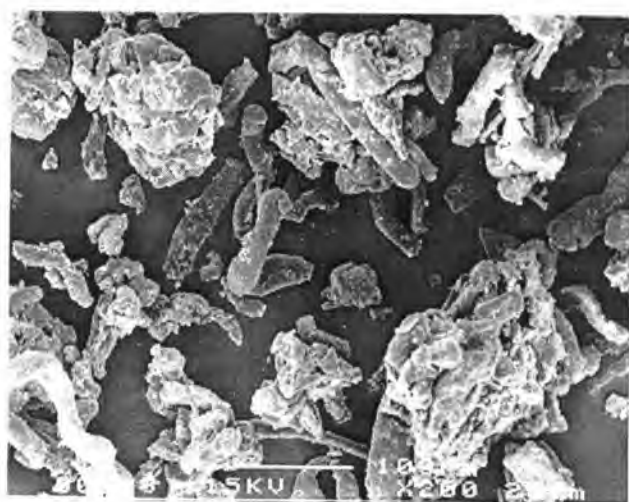


Figure 10 Photomicrographs of NaCMC_3 (A $\times 50$, B $\times 200$)



A



B

Figure 11 Photomicrographs of M_3 (A $\times 50$, B $\times 200$)

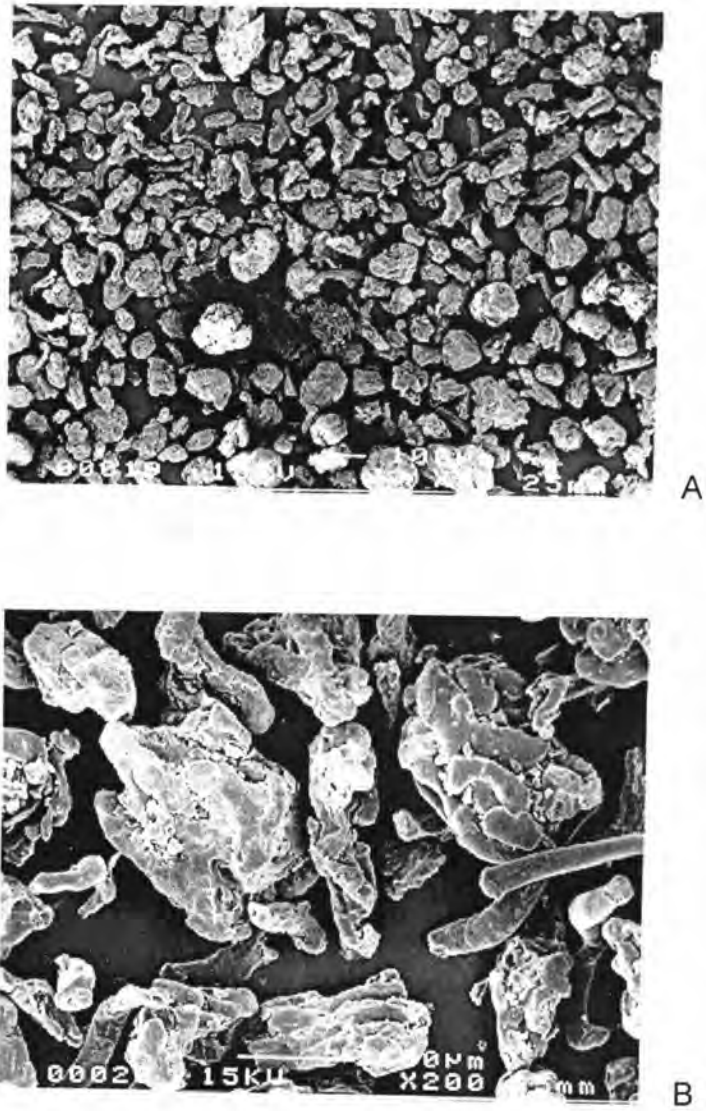


Figure 12 Photomicrographs of NaCMC₄ (A ×50 , B ×200)

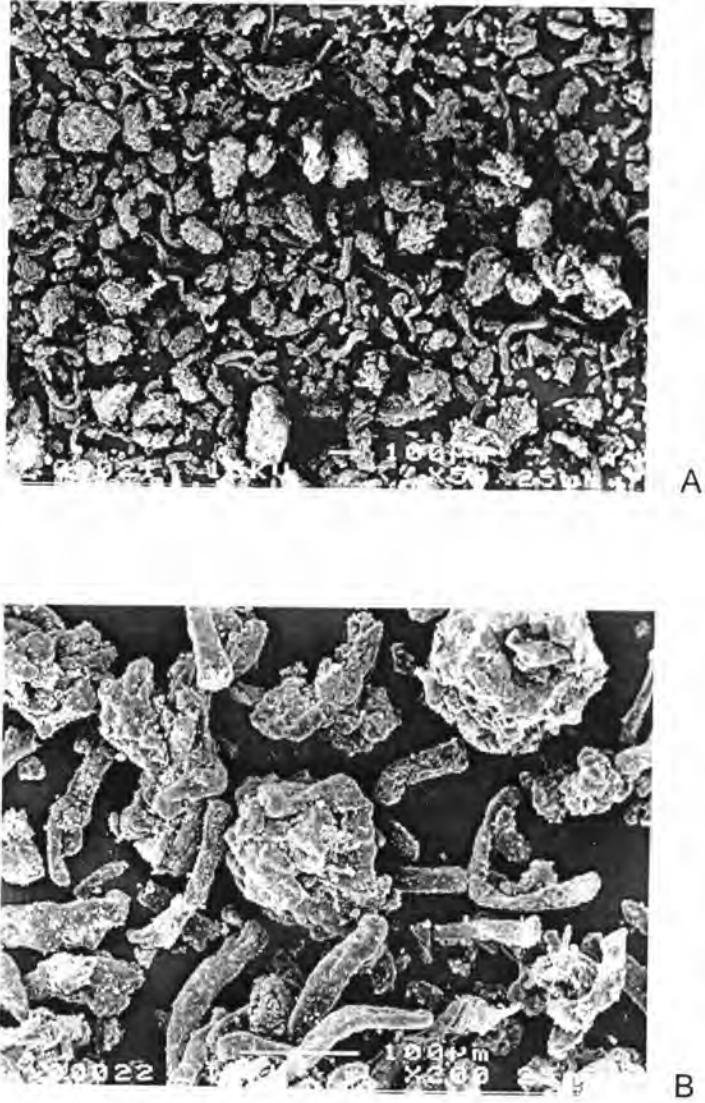


Figure 13 Photomicrographs of M₄ (A ×50 , B ×200)

modified sodium carboxymethylcellulose are summarized in Table 12 and graphically shown in Figure 14. The cumulative percent undersize and the curve of particle size distribution are presented in Table 27-34 and Figure 27-34 (Appendix II). The results indicated that modified sodium carboxymethylcellulose had larger particle size than sodium carboxymethylcellulose used as starting material except M_3 had smaller. It could be explained that the agglomeration of particles occurred during modified process. The average particle size (d_{vs}) decreased in the following order: $M_1 > M_2 > NaCMC_1 > NaCMC_3 > M_3 > NaCMC_2 > M_4 > NaCMC_4$. For d_{wm} , the order was the same as d_{vs} , except for M_3 and $NaCMC_2$, the latter appeared to be more. Specific surface area, on the other hand, showed the reverse in order from the data given above.

Table 12 The average particle size and specific surface area of sodium carboxymethylcellulose and modified sodium carboxymethylcellulose

Material	Average particle size* (μm) \pm SD		Specific surface area* ($\text{m}^2 \cdot \text{sec}$) \pm SD
	d_{vs} **	d_{wm} ***	
NaCMC ₁	52.52 \pm 7.03	136.99 \pm 1.57	0.1155 \pm 0.01
M ₁	108.85 \pm 1.20	162.44 \pm 0.88	0.0552 \pm 0.00
NaCMC ₂	42.30 \pm 0.77	118.39 \pm 12.38	0.1419 \pm 0.00
M ₂	72.15 \pm 10.51	140.08 \pm 1.75	0.0844 \pm 0.01
NaCMC ₃	46.85 \pm 0.60	124.45 \pm 1.79	0.1281 \pm 0.00
M ₃	43.48 \pm 1.75	106.19 \pm 3.60	0.1382 \pm 0.01
NaCMC ₄	38.60 \pm 0.38	91.69 \pm 0.45	0.1555 \pm 0.00
M ₄	39.58 \pm 1.38	101.67 \pm 0.96	0.1517 \pm 0.01

* The mean of two determinations

** d_{vs} = volume surface mean diameter (nd^3/nd^2)

*** d_{wm} = weight moment mean diameter (nd^4/nd^3)

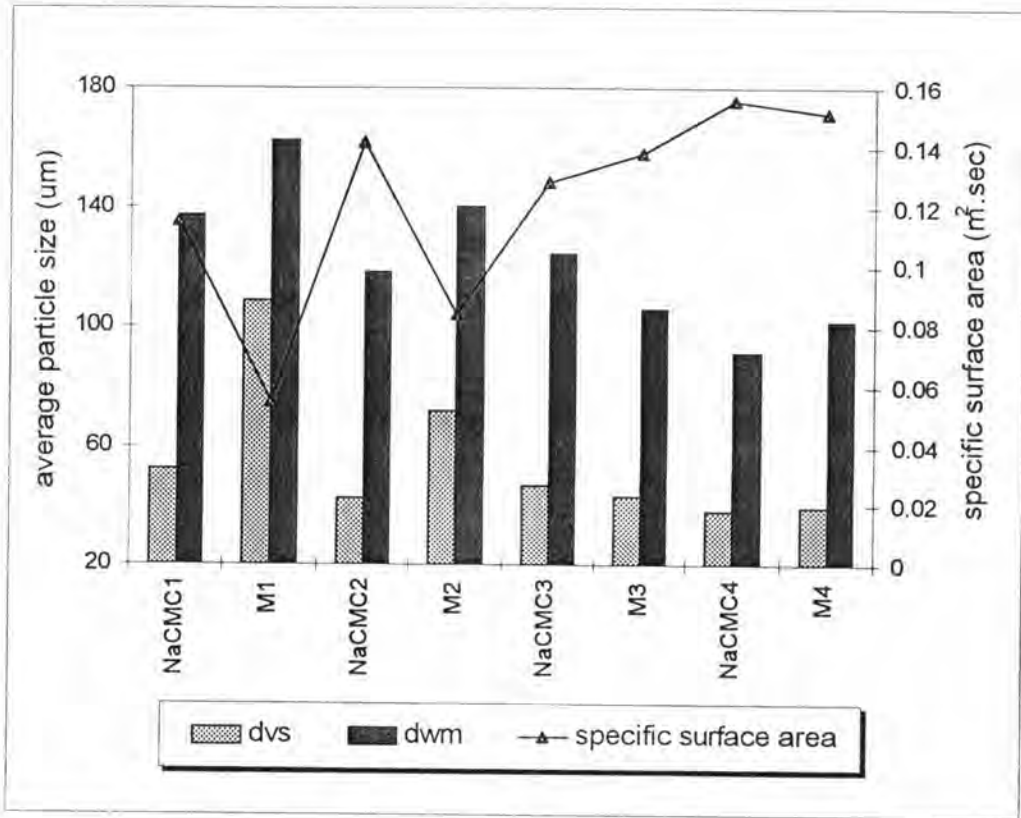


Figure 14 The average particle size and specific surface area of sodium carboxymethylcellulose and modified sodium carboxymethylcellulose

3.3 Bulk Density, Tapped Density and Percent Compressibility

The results of bulk density, tapped density and percent compressibility are presented in Table 13 and Figure 15. The bulk density decreased in the following order: $M_1 > M_4 > NaCMC_3 > NaCMC_2 > NaCMC_1 = NaCMC_4 > M_3 > M_2$. Bulk density of M_1 and M_4 were higher than starting material whereas that of M_2 and M_3 were lower than starting material. For tapped density, they could be ranked as follows: $NaCMC_3 > M_4 > NaCMC_1 = NaCMC_2 = NaCMC_4 > M_1 > M_3 > M_2$. It could be noticed that the modified sodium carboxymethylcellulose had lower tapped density than the starting materials except M_1 and M_4 had almost equal tapped density to the starting material. The percent compressibility was calculated from bulk and tapped density, and ranked as follows: $NaCMC_4 > NaCMC_1 > M_2 > NaCMC_3 >$

$\text{NaCMC}_2 > \text{M}_4 > \text{M}_3 > \text{M}_1$. However, these properties would not have much effect to the tablets prepared because these materials were used at rather low concentration in formulations.

Table 13 Bulk density, tapped density and percent compressibility of sodium carboxymethylcellulose and modified sodium carboxymethylcellulose

Material	Bulk density* (g/ml) \pm SD	Tapped density* (g/ml) \pm SD	Compressibility* (%) \pm SD
NaCMC ₁	0.46 \pm 0.01	0.67 \pm 0.00	30.76 \pm 0.92
M ₁	0.52 \pm 0.00	0.66 \pm 0.00	20.08 \pm 0.60
NaCMC ₂	0.49 \pm 0.01	0.67 \pm 0.02	27.51 \pm 1.90
M ₂	0.36 \pm 0.01	0.50 \pm 0.00	28.25 \pm 1.76
NaCMC ₃	0.50 \pm 0.01	0.70 \pm 0.01	27.71 \pm 1.51
M ₃	0.44 \pm 0.01	0.59 \pm 0.00	26.03 \pm 2.41
NaCMC ₄	0.46 \pm 0.01	0.67 \pm 0.02	31.40 \pm 2.76
M ₄	0.51 \pm 0.01	0.68 \pm 0.01	26.20 \pm 0.35

* The mean of three determinations

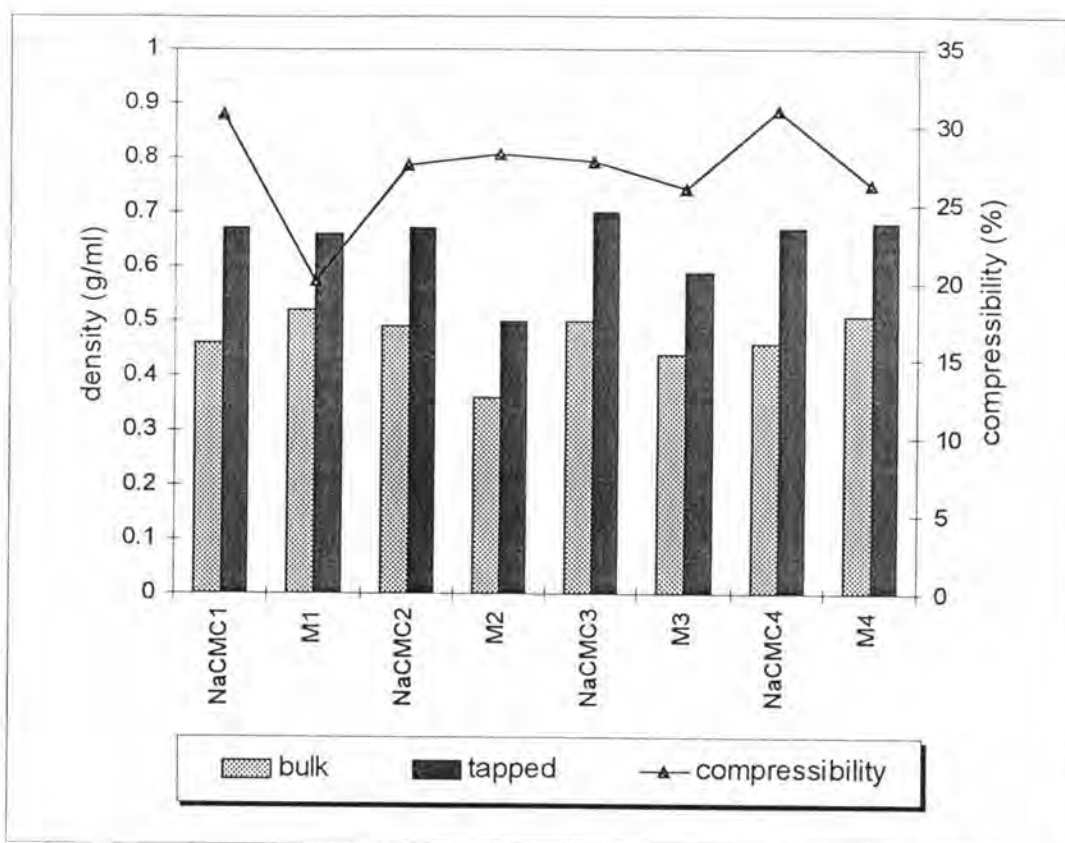


Figure 15 Bulk density, tapped density and percent compressibility of sodium carboxymethylcellulose and modified sodium carboxymethylcellulose

3.4 Moisture Determination

Moisture content of different sodium carboxymethylcellulose and modified sodium carboxymethylcellulose were given in Table 14 and Figure 16. The percentage of moisture content was in the range of 9.95 to 16.51. It could be noticed that the moisture content of these powders were somewhat high and the moisture content of modified sodium carboxymethylcellulose was higher than the starting material. The moisture content decreased in the following order: $M_1 \sim M_4 > M_3 > M_2 > \text{NaCMC}_1 > \text{NaCMC}_4 > \text{NaCMC}_2 > \text{NaCMC}_3$.

Table 14 Moisture content of sodium carboxymethylcellulose and modified sodium carboxymethylcellulose

Material	Moisture content* (%) \pm SD
NaCMC ₁	14.27 \pm 0.13
M ₁	16.51 \pm 0.91
NaCMC ₂	13.24 \pm 1.23
M ₂	14.52 \pm 0.38
NaCMC ₃	9.95 \pm 1.74
M ₃	16.17 \pm 0.34
NaCMC ₄	13.58 \pm 0.38
M ₄	16.50 \pm 1.40

* The mean of three determinations

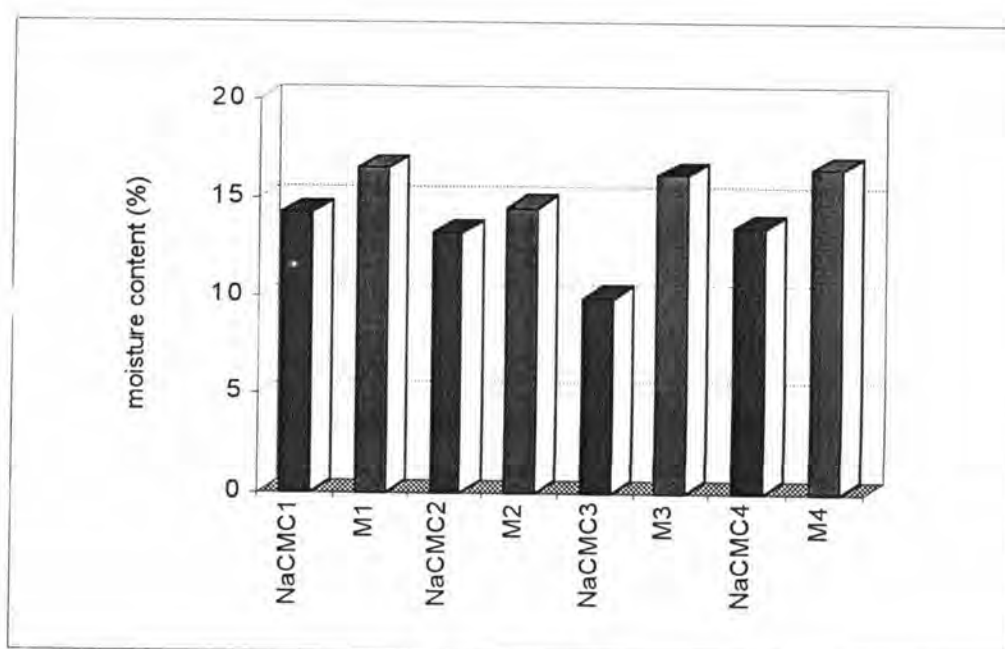


Figure 16 Moisture content of sodium carboxymethylcellulose and modified sodium carboxymethylcellulose

4. Evaluation of Physical Properties of Modified Sodium Carboxymethylcellulose Compared with Sodium Carboxymethylcellulose Used as Starting Materials and Commercial Disintegrants

Tablet disintegration was depending on several factors. In many cases, disintegration was caused by a water uptake in tablet. After this absorption, there was a rupture of intraparticle cohesive forces, which may be increased by the swelling of disintegrant. The more important factors to account for the efficiency of a disintegrant were therefore wetting, water uptake which permit the penetration of gastric juice in tablet, and swelling which increase tablet disintegration. These are the different factors which were studied on several disintegrants.

Certain physical parameters were determined for modified sodium carboxymethylcellulose in comparison with sodium carboxymethylcellulose used as starting materials and commercial disintegrants in an attempt to predict their relative efficiency as tablet disintegrant. These parameters were water uptake, swelling of particles, sedimentation volume and hydration capacity.

4.1 Water Uptake

The results of water uptake study of various sodium carboxymethylcellulose, modified sodium carboxymethylcellulose including commercial disintegrant powders are presented in Table 15 and 16 and those are graphically shown in Figure 17-20. The comparison of the volume of water uptake of powders in this study shown that the volume of water uptake decreased in the following order: Primojel[®] > Ac-di-sol[®] > M₂ > NaCMC₂ > M₄ > M₃ > NaCMC₃ > Nymcel[®] > NaCMC₁ > M₁ > NaCMC₄ > corn starch. And the rate of water uptake were ranked as follows: Primojel[®] > Ac-di-sol[®] > M₂ > M₃ > NaCMC₂ > corn starch > M₁ > M₄ > Nymcel[®] > NaCMC₄ > NaCMC₁ >

Table 15 The volume of water uptake of disintegrants at various time intervals

Time (min)	Volume of water uptake* (ml) \pm SD							
	NaCMC ₁	M ₁	NaCMC ₂	M ₂	NaCMC ₃	M ₃	NaCMC ₄	M ₄
0.00	0.000 \pm 0.000	0.000 \pm 0.000	0.000 \pm 0.000	0.000 \pm 0.000	0.000 \pm 0.000	0.000 \pm 0.000	0.000 \pm 0.000	0.000 \pm 0.000
0.25	0.043 \pm 0.024	0.075 \pm 0.022	0.083 \pm 0.035	0.162 \pm 0.025	0.032 \pm 0.019	0.136 \pm 0.013	0.045 \pm 0.023	0.063 \pm 0.025
0.50	0.043 \pm 0.020	0.065 \pm 0.031	0.069 \pm 0.050	0.208 \pm 0.013	0.010 \pm 0.032	0.145 \pm 0.012	0.038 \pm 0.024	0.111 \pm 0.030
0.75	0.045 \pm 0.021	0.090 \pm 0.035	0.115 \pm 0.054	0.248 \pm 0.016	0.021 \pm 0.027	0.153 \pm 0.012	0.035 \pm 0.031	0.149 \pm 0.014
1.00	0.049 \pm 0.022	0.091 \pm 0.037	0.120 \pm 0.059	0.275 \pm 0.013	0.027 \pm 0.027	0.158 \pm 0.011	0.035 \pm 0.031	0.165 \pm 0.005
1.50	0.067 \pm 0.023	0.097 \pm 0.044	0.133 \pm 0.061	0.300 \pm 0.015	0.039 \pm 0.025	0.167 \pm 0.010	0.037 \pm 0.032	0.184 \pm 0.001
2.00	0.067 \pm 0.023	0.103 \pm 0.045	0.143 \pm 0.064	0.319 \pm 0.020	0.053 \pm 0.028	0.175 \pm 0.011	0.043 \pm 0.028	0.197 \pm 0.003
2.50	0.073 \pm 0.024	0.105 \pm 0.046	0.150 \pm 0.066	0.335 \pm 0.022	0.063 \pm 0.029	0.181 \pm 0.012	0.047 \pm 0.014	0.203 \pm 0.003
3.00	0.083 \pm 0.024	0.113 \pm 0.050	0.159 \pm 0.065	0.346 \pm 0.025	0.078 \pm 0.033	0.190 \pm 0.011	0.054 \pm 0.024	0.212 \pm 0.004
3.50	0.096 \pm 0.024	0.121 \pm 0.049	0.173 \pm 0.065	0.357 \pm 0.024	0.093 \pm 0.034	0.202 \pm 0.011	0.065 \pm 0.019	0.224 \pm 0.005
4.00	0.112 \pm 0.024	0.133 \pm 0.050	0.188 \pm 0.065	0.375 \pm 0.026	0.110 \pm 0.036	0.215 \pm 0.012	0.078 \pm 0.021	0.235 \pm 0.003
4.50	0.125 \pm 0.023	0.144 \pm 0.051	0.198 \pm 0.065	0.387 \pm 0.029	0.127 \pm 0.037	0.229 \pm 0.012	0.090 \pm 0.026	0.246 \pm 0.003
5.00	0.139 \pm 0.022	0.153 \pm 0.049	0.211 \pm 0.067	0.400 \pm 0.026	0.140 \pm 0.039	0.242 \pm 0.011	0.103 \pm 0.030	0.256 \pm 0.002
10.00	0.235 \pm 0.026	0.229 \pm 0.056	0.303 \pm 0.073	0.497 \pm 0.019	0.256 \pm 0.046	0.344 \pm 0.012	0.203 \pm 0.015	0.344 \pm 0.003
15.00	0.308 \pm 0.033	0.286 \pm 0.062	0.381 \pm 0.068	0.573 \pm 0.018	0.338 \pm 0.054	0.413 \pm 0.016	0.272 \pm 0.040	0.411 \pm 0.005
20.00	0.368 \pm 0.040	0.333 \pm 0.064	0.448 \pm 0.066	0.638 \pm 0.020	0.410 \pm 0.065	0.473 \pm 0.021	0.326 \pm 0.012	0.463 \pm 0.012
25.00	0.421 \pm 0.045	0.379 \pm 0.067	0.509 \pm 0.070	0.700 \pm 0.023	0.453 \pm 0.066	0.526 \pm 0.021	0.371 \pm 0.024	0.513 \pm 0.015
30.00	0.469 \pm 0.046	0.419 \pm 0.068	0.565 \pm 0.071	0.760 \pm 0.031	0.500 \pm 0.069	0.571 \pm 0.029	0.412 \pm 0.021	0.558 \pm 0.016
40.00	0.546 \pm 0.042	0.485 \pm 0.066	0.633 \pm 0.080	0.866 \pm 0.037	0.592 \pm 0.110	0.631 \pm 0.039	0.485 \pm 0.031	0.646 \pm 0.015
50.00	0.625 \pm 0.047	0.562 \pm 0.070	0.788 \pm 0.104	0.962 \pm 0.038	0.669 \pm 0.130	0.713 \pm 0.043	0.549 \pm 0.021	0.725 \pm 0.009
60.00	0.692 \pm 0.047	0.618 \pm 0.080	0.873 \pm 0.125	1.048 \pm 0.040	0.751 \pm 0.144	0.772 \pm 0.027	0.607 \pm 0.013	0.820 \pm 0.039

* The mean of three determinations

Table 15 (cont.)

Time (min)	Volume of water uptake* (ml) ± SD			
	Ac-di-sol®	Nymcel®	Primojel®	corn starch
0.00	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
0.25	0.430 ± 0.032	0.060 ± 0.006	0.590 ± 0.122	0.030 ± 0.021
0.50	0.528 ± 0.007	0.068 ± 0.007	0.750 ± 0.159	0.148 ± 0.024
0.75	0.608 ± 0.080	0.125 ± 0.000	0.948 ± 0.161	0.225 ± 0.016
1.00	0.747 ± 0.090	0.140 ± 0.000	1.197 ± 0.131	0.265 ± 0.020
1.50	0.960 ± 0.175	0.170 ± 0.000	1.583 ± 0.107	0.295 ± 0.018
2.00	1.081 ± 0.146	0.195 ± 0.004	1.884 ± 0.091	0.303 ± 0.018
2.50	1.218 ± 0.144	0.208 ± 0.004	2.135 ± 0.101	0.297 ± 0.015
3.00	1.351 ± 0.134	0.220 ± 0.004	2.364 ± 0.104	0.293 ± 0.027
3.50	1.488 ± 0.100	0.237 ± 0.004	2.568 ± 0.116	0.290 ± 0.032
4.00	1.615 ± 0.079	0.257 ± 0.004	2.748 ± 0.124	0.293 ± 0.025
4.50	1.728 ± 0.057	0.275 ± 0.000	2.905 ± 0.121	0.294 ± 0.026
5.00	1.825 ± 0.053	0.287 ± 0.004	3.061 ± 0.136	0.295 ± 0.029
10.00	2.511 ± 0.042	0.390 ± 0.107	4.418 ± 0.403	0.305 ± 0.032
15.00	2.948 ± 0.031	0.441 ± 0.009	> 5.000	0.315 ± 0.024
20.00	3.278 ± 0.015	0.490 ± 0.007	-	0.325 ± 0.024
25.00	3.558 ± 0.040	0.527 ± 0.004	-	0.330 ± 0.020
30.00	3.795 ± 0.050	0.558 ± 0.001	-	0.330 ± 0.012
40.00	4.145 ± 0.062	0.621 ± 0.006	-	0.330 ± 0.011
50.00	4.438 ± 0.055	0.680 ± 0.007	-	0.330 ± 0.014
60.00	4.685 ± 0.035	0.747 ± 0.018	-	0.330 ± 0.000

* The mean of three determinations

Table 16 The rate of water uptake of disintegrants at various time intervals

Time (min)	Rate of water uptake* (ml/min)											corn starch
	NaCMC ₁	M ₁	NaCMC ₂	M ₂	NaCMC ₃	M ₃	NaCMC ₄	M ₄	Ac-dl-sol [®]	Nymcel [®]	Primojel [®]	
0.00	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.25	0.173	0.300	0.333	0.647	0.128	0.540	0.180	0.253	1.720	0.240	2.360	0.120
0.50	0.085	0.169	0.198	0.415	0.019	0.290	0.075	0.222	1.055	0.195	1.500	0.295
0.75	0.060	0.120	0.153	0.331	0.028	0.204	0.047	0.199	0.811	0.167	1.264	0.300
1.00	0.049	0.091	0.120	0.275	0.027	0.158	0.035	0.165	0.747	0.140	1.197	0.265
1.50	0.038	0.064	0.089	0.200	0.026	0.111	0.025	0.123	0.620	0.113	1.056	0.197
2.00	0.033	0.051	0.071	0.160	0.027	0.087	0.021	0.098	0.540	0.098	0.942	0.151
2.50	0.029	0.042	0.060	0.134	0.025	0.073	0.019	0.081	0.487	0.083	0.854	0.119
3.00	0.028	0.038	0.053	0.115	0.026	0.063	0.018	0.071	0.450	0.073	0.788	0.098
3.50	0.027	0.034	0.049	0.102	0.027	0.058	0.018	0.064	0.425	0.068	0.734	0.083
4.00	0.028	0.033	0.047	0.094	0.027	0.054	0.019	0.059	0.404	0.064	0.687	0.073
4.50	0.028	0.032	0.044	0.086	0.028	0.051	0.020	0.055	0.384	0.061	0.645	0.065
5.00	0.028	0.031	0.042	0.080	0.028	0.048	0.021	0.051	0.365	0.057	0.612	0.059
10.00	0.023	0.023	0.030	0.050	0.026	0.034	0.020	0.034	0.251	0.039	0.442	0.030
15.00	0.021	0.019	0.025	0.038	0.023	0.028	0.018	0.027	0.197	0.029	0.356	0.021
20.00	0.018	0.017	0.022	0.032	0.021	0.024	0.016	0.023	0.164	0.024	-	0.016
25.00	0.017	0.015	0.020	0.028	0.018	0.021	0.015	0.021	0.142	0.021	-	0.013
30.00	0.016	0.014	0.019	0.025	0.017	0.019	0.014	0.019	0.126	0.019	-	0.011
40.00	0.014	0.012	0.017	0.022	0.015	0.016	0.012	0.016	0.104	0.016	-	0.008
50.00	0.013	0.011	0.016	0.019	0.013	0.014	0.011	0.014	0.089	0.014	-	0.007
60.00	0.012	0.010	0.015	0.017	0.013	0.013	0.010	0.014	0.078	0.012	-	0.005

* The mean of three determinations

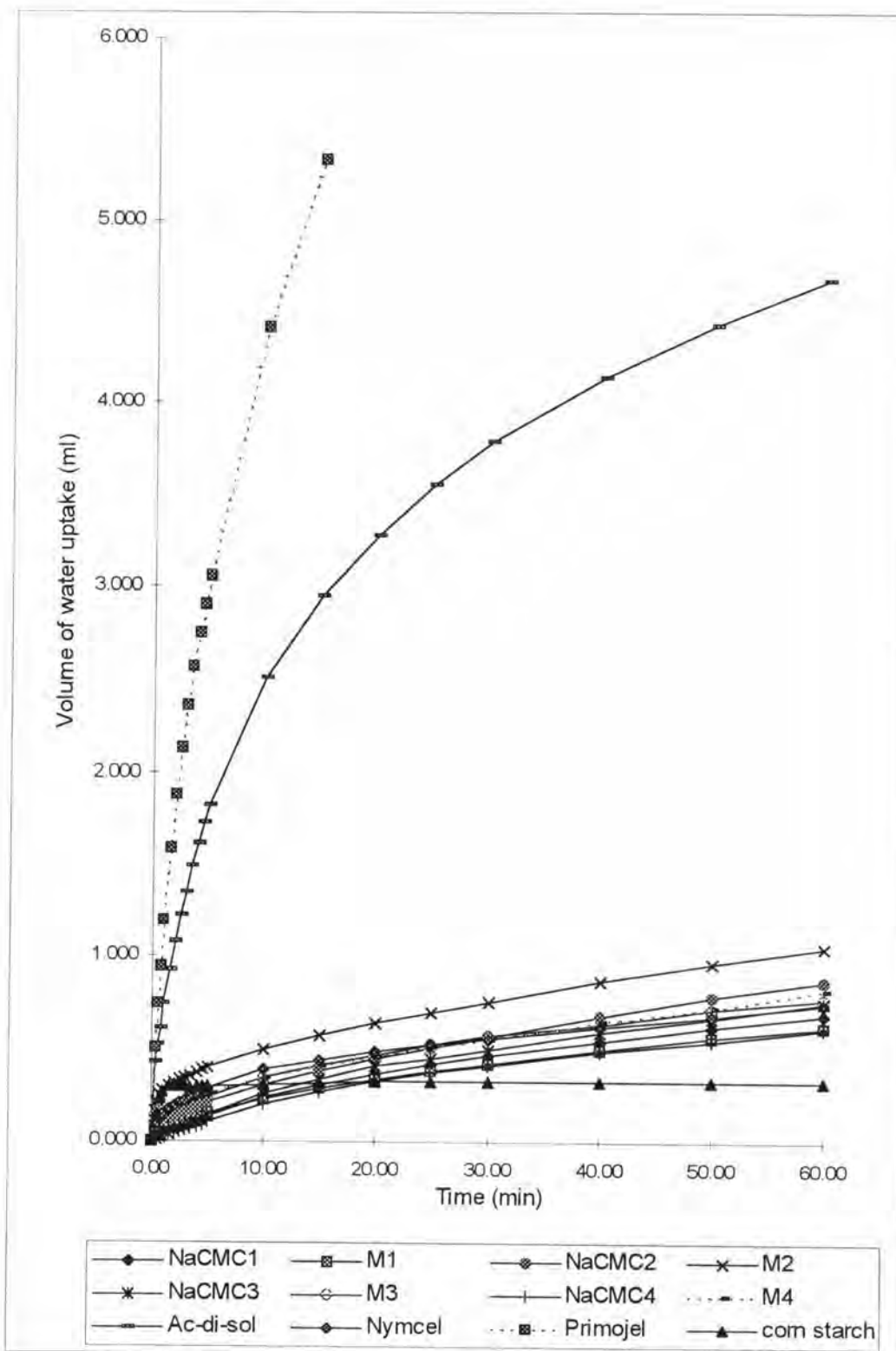


Figure 17 The volume of water uptake profile of disintegrants

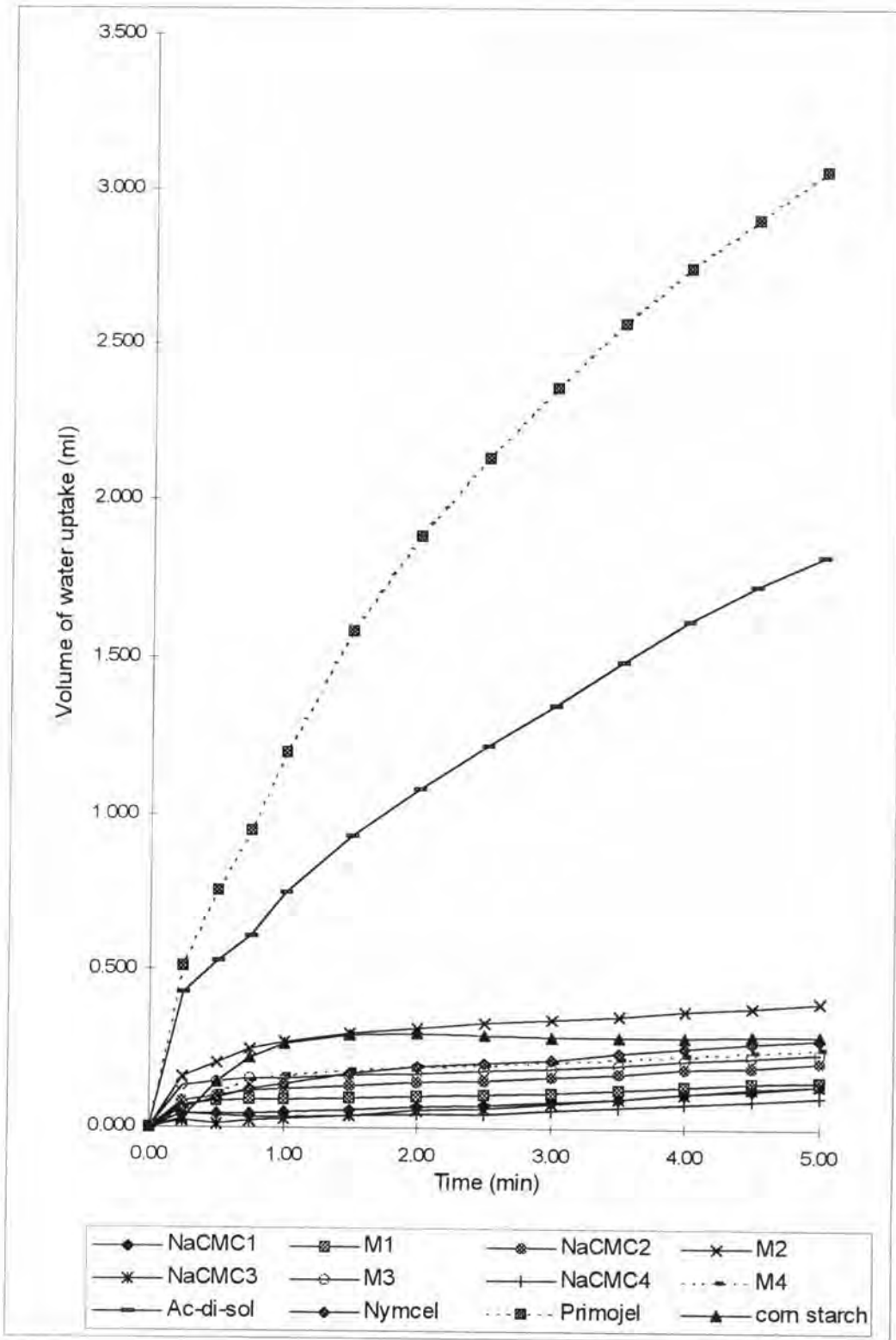


Figure 18 The volume of water uptake profile of disintegrants at various time intervals within the first 5 minutes

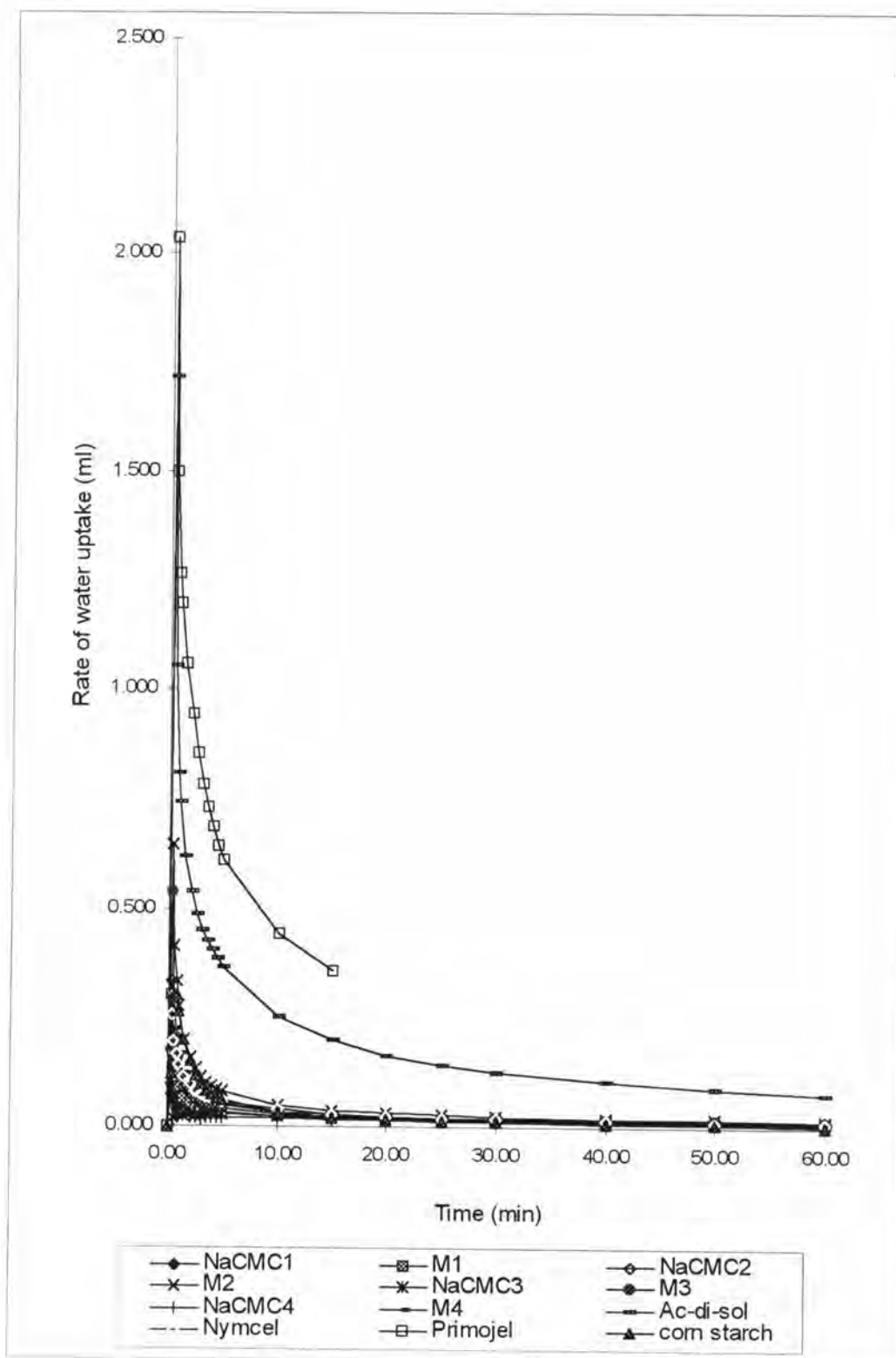


Figure 19 The rate of water uptake profile of disintegrants

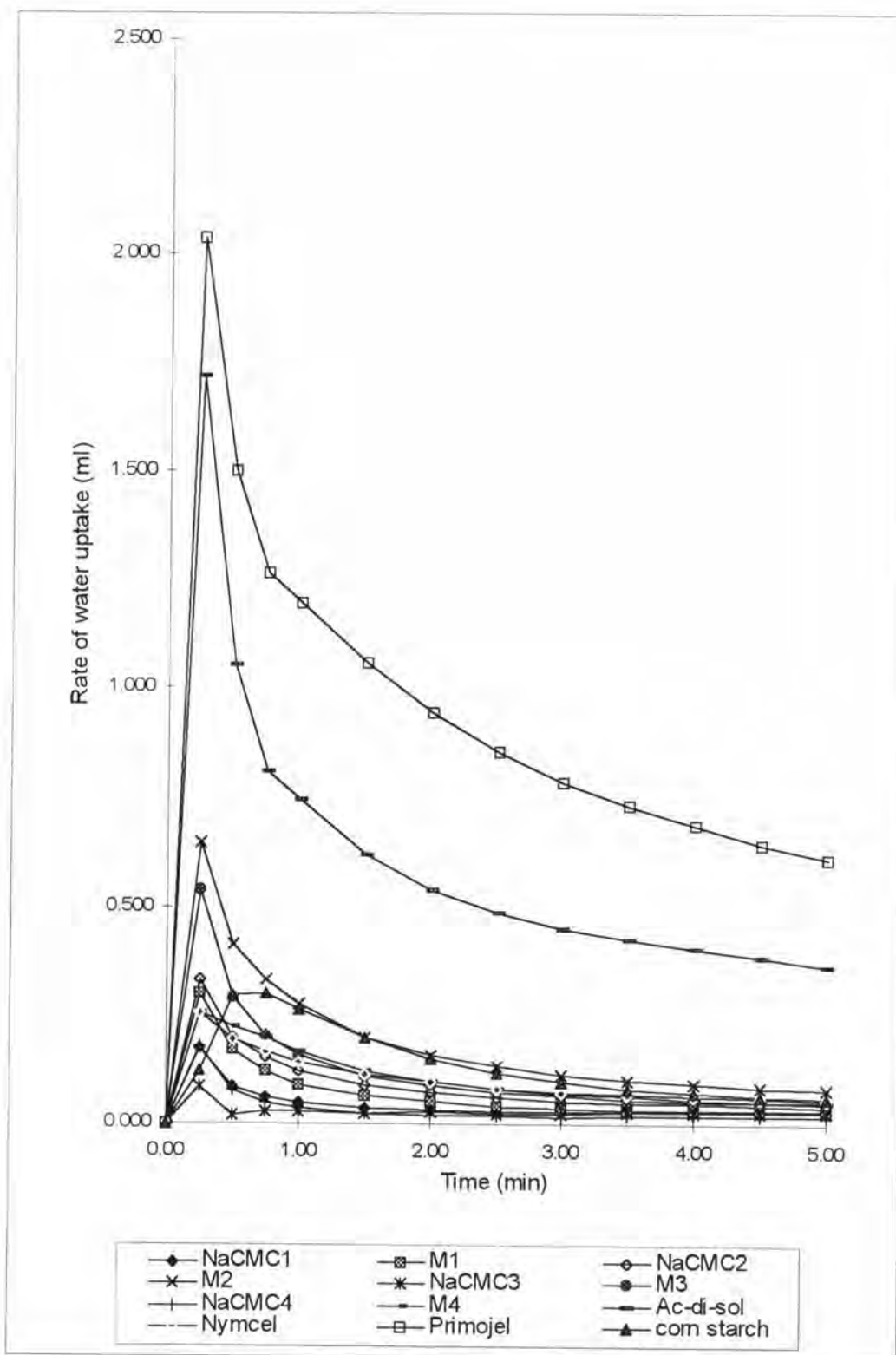


Figure 20 The rate of water uptake profile of disintegrants at various time intervals within the first 5 minutes

NaCMC₃. The statistical differences are illustrated in Table 43-46 (Appendix III). The rate of water uptake of disintegrants decreased against time.

Two of the studied disintegrants, Primojel[®] and Ac-di-sol[®] showed the volume and the rate of water uptake much more than the others and significant differences ($p < 0.05$). Water penetration was clearly fastest and total water uptake was greatest for Primojel[®]. Ac-di-sol[®] showed significantly lower rate and amount of water uptake when compared to Primojel[®]. This could be attributed to the partial water solubility of Ac-di-sol[®] resulting in a viscous barrier forming during water penetration.

Sodium carboxymethylcellulose and modified sodium carboxymethylcellulose were superior to corn starch in terms of the volume of water uptake. The small amount of water uptake by sodium carboxymethylcellulose, modified sodium carboxymethylcellulose and Nymcel[®] could be explained by the fact that these particles swell on contact with water, forming a viscous gel barrier, blocking the pores of particles and thus hindering further water uptake. However, the volume and the rate of water uptake of modified sodium carboxymethylcellulose was higher than that of sodium carboxymethylcellulose used as starting material except the volume of water uptake of M₁ appeared to be less than starting material but no significant difference. It might be due to the viscosity of M₁ was higher than NaCMC₁, therefore the effect of viscous gel barrier of M₁ on water uptake was also high. The possible explanation for the higher volume and rate of water uptake of modified sodium carboxymethylcellulose when compared to that of sodium carboxymethylcellulose was the cross-linking reaction resulting in the decreased water solubility of modified sodium carboxymethylcellulose, therefore the viscous gel formation around the particles was less and slower than the starting material. For corn starch, it showed the fourth order of the rate of water uptake at first minute interval, then gradually decreased and finally showed the lowest rate.

Water uptake had been an important mechanism of tablet disintegrant. In order to validate the tablet disintegration, the first important step of sequence was water to be drawn up to the tablet matrix which called wicking. The ability of particles to draw up water into porous network of a tablet was essential for effective disintegration (Khan and Rhodes, 1975) and the rate of wicking or water uptake was responsible at least in part for disintegrant action. Bolhius et al. (1981) concluded that if wetting of the disintegrant particles was slow, disintegration of tablet was slow. They have not only implicated the extent of water uptake is of critical importance for a number of the disintegrants. Sakr et al. (1975) and Sheen and Kim (1989) examined the rate of water absorption of disintegrants and found that it generally correlated positively with the speed of disintegration, but Wan and Prasad (1989) found that water uptake alone does not determine the disintegration process.

Puech and Serraro, 1970 cited in Lowenthal (1972) suggested that the disintegrants that absorb about 20% water and insoluble in water are said to be good disintegrant. Those that absorb about 40% water and are soluble in water increase disintegration time and those that absorb water poorly are poor disintegrants.

4.2 Swelling of Particles

The swelling of disintegrants particles in water and methanol were recorded during a maximum of 20 minutes. The results of particle size analysis as a function of time are shown in Table 17.

The average particle size of various sodium carboxymethylcellulose in water was not possible to carry on the measurement after some minutes because the particles dissolved in medium and formed gel, then the agglomeration was occurred. That of various sodium carboxymethylcellulose in methanol was in the range of 13.98 to 33.84 μm

Table 17 The average particle size of disintegrants in water and methanol

Material	Time (min)	Average particle size* (μm)			
		d_{vs}		d_{wm}	
		H ₂ O	MeOH	H ₂ O	MeOH
NaCMC ₁	1	**	33.84	**	66.69
	2	**	14.38	**	52.23
	3	**	14.88	**	60.79
	5	**	24.01	**	42.41
	10	**	20.40	**	33.44
NaCMC ₂	1	242.96	27.17	391.51	107.88
	2	164.50	26.21	246.86	106.40
	3	**	26.39	**	108.55
	5	**	25.87	**	105.04
	10	**	25.66	**	108.50
NaCMC ₃	1	265.72	13.98	380.04	20.61
	2	254.47	16.28	367.21	25.82
	3	**	-	**	-
	5	**	-	**	-
	10	**	-	**	-
NaCMC ₄	1	281.49	23.38	399.32	87.97
	2	136.75	19.70	258.28	71.53
	3	**	16.74	**	61.66
	5	**	17.58	**	60.55
	10	**	32.49	**	48.39
M ₁	1	121.98	57.51	268.81	170.07
	2	100.64	53.91	205.65	164.18
	3	98.91	52.69	204.30	163.01
	5	94.24	49.72	188.98	156.82
	10	89.14	47.02	172.78	152.55
	15	86.00	45.24	164.09	148.60
	20	82.38	44.77	153.26	145.31

Table 17 (cont.)

Material	Time (min)	Average particle size* (μm)			
		d_{vs}		d_{wm}	
		H ₂ O	MeOH	H ₂ O	MeOH
M ₂	1	147.22	58.71	279.01	209.00
	2	145.34	48.94	278.41	176.46
	3	145.74	46.82	276.96	165.80
	5	145.12	43.81	275.60	154.70
	10	142.92	31.62	274.22	114.80
	15	-	27.82	-	101.79
M ₃	1	133.25	30.10	233.19	102.53
	2	126.89	28.25	214.41	93.18
	3	125.79	27.24	212.86	87.99
	5	122.54	50.03	203.35	83.31
	10	119.42	46.22	194.86	76.43
	15	117.65	47.15	190.07	70.21
	20	116.33	44.71	186.03	65.09
M ₄	1	143.60	27.60	271.34	98.89
	2	139.09	58.28	264.71	87.77
	3	138.33	55.68	263.42	83.81
	5	137.64	49.90	259.80	80.63
	10	134.05	46.26	249.93	73.90
	15	129.70	44.78	240.34	72.04
	20	128.91	42.85	236.95	68.27
M ₃ (no Na ₃ P ₃ O ₉)***	1	233.38	70.32	331.52	113.89
	2	204.75	60.86	274.30	93.01
	3	**	57.69	**	87.84
	5	**	53.03	**	78.78
	10	**	47.75	**	70.60
	15	**	45.01	**	66.73
	20	**	46.53	**	64.42
Ac-di-sol [®]	1	37.50	15.64	91.23	57.86
	2	36.21	15.39	86.58	57.08
	3	36.11	15.37	86.26	57.07
	5	36.09	15.32	85.99	57.35
	10	-	15.30	-	57.25

Table 17 (cont.)

Material	Time (min)	Average particle size* (μm)			
		d_{vs}		d_{wm}	
		H ₂ O	MeOH	H ₂ O	MeOH
Nymcel [®]	1	62.78	21.01	155.26	84.28
	2	59.73	20.24	143.42	82.12
	3	59.04	19.59	142.00	77.58
	5	57.79	19.42	134.01	76.41
	10	56.46	19.63	130.94	82.60
	15	55.35	-	124.69	-
Primojel [®]	1	54.41	38.39	107.66	45.38
	2	56.25	37.76	111.89	44.72
	3	56.81	37.99	113.39	44.99
	5	57.09	38.06	112.20	44.95
	10	57.77	38.17	112.13	45.11
corn starch	1	5.55	7.92	18.34	19.98
	2	5.61	15.87	16.92	20.96
	3	5.58	15.73	16.89	20.70
	5	5.76	-	17.18	-
	10	5.79	-	25.61	-
	15	5.97	-	27.77	-

* The mean of two determinations

** Non-detectable because the particles formed gel and agglomerated

*** NaCMC₃ which treated with the same condition of cross-linking reaction but no added sodium trimetaphosphate

(d_{vs}) and 20.61 to 108.55 μm (d_{wm}). In methanol the average particle size of sodium carboxymethylcellulose almost equal as the function of time. For example, the average particle size (d_{vs}) of NaCMC₂ at 1, 2, 3, 5 and 10 minutes was 27.17, 26.21, 26.39, 25.87 and 25.66 μm , respectively. And d_{wm} of NaCMC₂ was 107.88, 106.40, 108.55, 105.04 and 108.50 μm at the time of 1, 2, 3, 5 and 10 minutes, respectively. When compared to the average particle size of dry powder of NaCMC₂ (see section 3.2), the dispersion of NaCMC₂ in methanol had smaller size than dry powder. The d_{vs} of dry powder of NaCMC₂ was 42.30 and d_{wm} was 118.39 μm .

At 1 minute, d_{vs} of M_1 , M_2 , M_3 and M_4 in water were 121.98, 147.22, 133.25 and 143.60 μm , respectively and d_{wm} of these materials were 268.81, 279.01, 233.19 and 271.34 μm , respectively. From the previous section (3.2), d_{vs} of dry powder of M_1 , M_2 , M_3 and M_4 were 108.85, 72.15, 43.48 and 39.58 μm , respectively and d_{wm} of these were 162.44, 140.08, 106.19 and 101.67 μm , respectively. It can be noticed that these particle swell in water and the swelling occurred within 1 minute when contact with water. When the time was longer, the particle size decreased because these particle partially dissolved in water. Among the modified sodium carboxymethylcellulose, M_4 was the most swellable particles about 3.6 times of its original d_{vs} and 2.7 times of its original d_{wm} . In methanol, d_{vs} of M_1 , M_2 , M_3 and M_4 at 1 minutes were 57.51, 58.71, 30.10 and 27.60 μm , respectively and d_{wm} of these were 170.07, 209.00, 102.53 and 98.89 μm , respectively. These results showed that the modified sodium carboxymethylcellulose did not swell in methanol.

The result of sodium carboxymethylcellulose which treated with the same condition of cross-linking reaction but no added sodium trimetaphosphate (M_3 (no $\text{Na}_3\text{P}_3\text{O}_9$)) was like to that of NaCMC₃. That was the

particle dissolved in water, formed gel and then agglomerated. So, it could not be determined.

For Ac-di-sol[®], Nymcel[®], Primojel[®] and corn starch, the particle size (d_{vs}) in water at 1 minute were 37.50, 62.78, 54.41 and 5.55 μm , respectively and d_{wm} of these were 91.23, 155.26, 107.66 and 18.34 μm , respectively. These particles were smaller than modified sodium carboxymethylcellulose. The particle size (d_{vs}) of Ac-di-sol[®] and Nymcel[®], in dry powder were 23.1 and 47.3 μm , respectively and d_{wm} of these were 38.5 and 69.2 μm , respectively (Kiatmonkong, 1989). For Primojel[®] and corn starch, the average particle size was 42 and 17 μm , respectively (Wade and Weller, 1994). Therefore, it can be conclude that the swelling of Ac-di-sol[®], Nymcel[®] and Primojel[®] in water was occurred within 1 minute like to that of modified sodium carboxymethylcellulose and corn starch did not swell when contacted with water.

The swelling study by video recording method showed that in the case of Ac-di-sol[®], swelling was complete in 5-6 second. Upon hydration, smaller particles and fibres grew in size assuming larger cylindrical shapes. In about 45 second time, large swollen particles were formed. Some merged together, others dissolved, while still others remained unchanged. The dissolving portions could be the non-crosslinked components of the sodium carboxymethylcellulose polymer. Swelling of Nymcel[®] particles extended up to about 30 second although most of it occurred in the first 4 second after contact with water. The particles became transparent, enlarged in size yet retained their general shape characteristics. Smaller fragments of the material however dissolved or integrated with other swollen masses in their vicinity (Wan and Prasad, 1990).

Starch is the most common disintegrating agent in use today. It was once assumed that the function of starch as a disintegrant depended on its swelling when wetted. However, it has been shown that starch does not swell when exposed to water at the temperature found in gastric fluids. It has been suggested that the disintegrating action of starch is not due to swelling but rather arises from capillary action (Curlin, 1955 cited in Visavarungroj and Remon, 1990).

Swelling is generally thought to be one of the mechanisms by which disintegration of tablets takes place (Lowenthal, 1973; Fakouhi, Billups and Sager, 1963 cited in Wan and Prasad, 1990). Gum, clay and some cellulose derivatives swell on contact with water, creating pressures between particles of the tablet and bringing about disintegration.

Swelling of tablet excipient particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particle or hydration of macromolecules. The liquid enters the particles through pores and binds to large molecules, breaking hydrogen bonds and resulting in the swelling of the particle (Wan and Prasad, 1990).

4.3 Sedimentation Volume

Although many disintegrant studies could not correlate rank-order sedimentation volume with disintegrant efficiency, in fact, sedimentation volume are still used to simply explain about swelling volume of disintegrant powders. Rudnic et al. (1982) stated that sedimentation volume was poorly correlated with the relative activity of the disintegrants. The sedimentation volume of various disintegrants are shown in Table 18 and Figure 21. They were ranked as the following: Primojel® > Ac-di-sol® > corn starch. The statistical differences are shown in Table 47 and 48 (Appendix III). And the significantly difference ($p < 0.05$) was observed in the sedimentation volume

of Primojel[®], Ac-di-sol[®] and corn starch. The determination of sedimentation volume of Nymcel[®], sodium carboxymethylcellulose and modified sodium carboxymethylcellulose could not be achieved because these materials partially dissolved in water and formed viscous gel.

Table 18 The sedimentation volume of disintegrants

Material	Sedimentation volume* (ml/gm) \pm SD
NaCMC ₁	non-detectable
M ₁	non-detectable
NaCMC ₂	non-detectable
M ₂	non-detectable
NaCMC ₃	non-detectable
M ₃	non-detectable
NaCMC ₄	non-detectable
M ₄	non-detectable
Ac-di-sol [®]	13.37 \pm 0.15
Nymcel [®]	non-detectable
Primojel [®]	17.83 \pm 0.12
corn starch	1.32 \pm 0.01

* The mean of three determinations

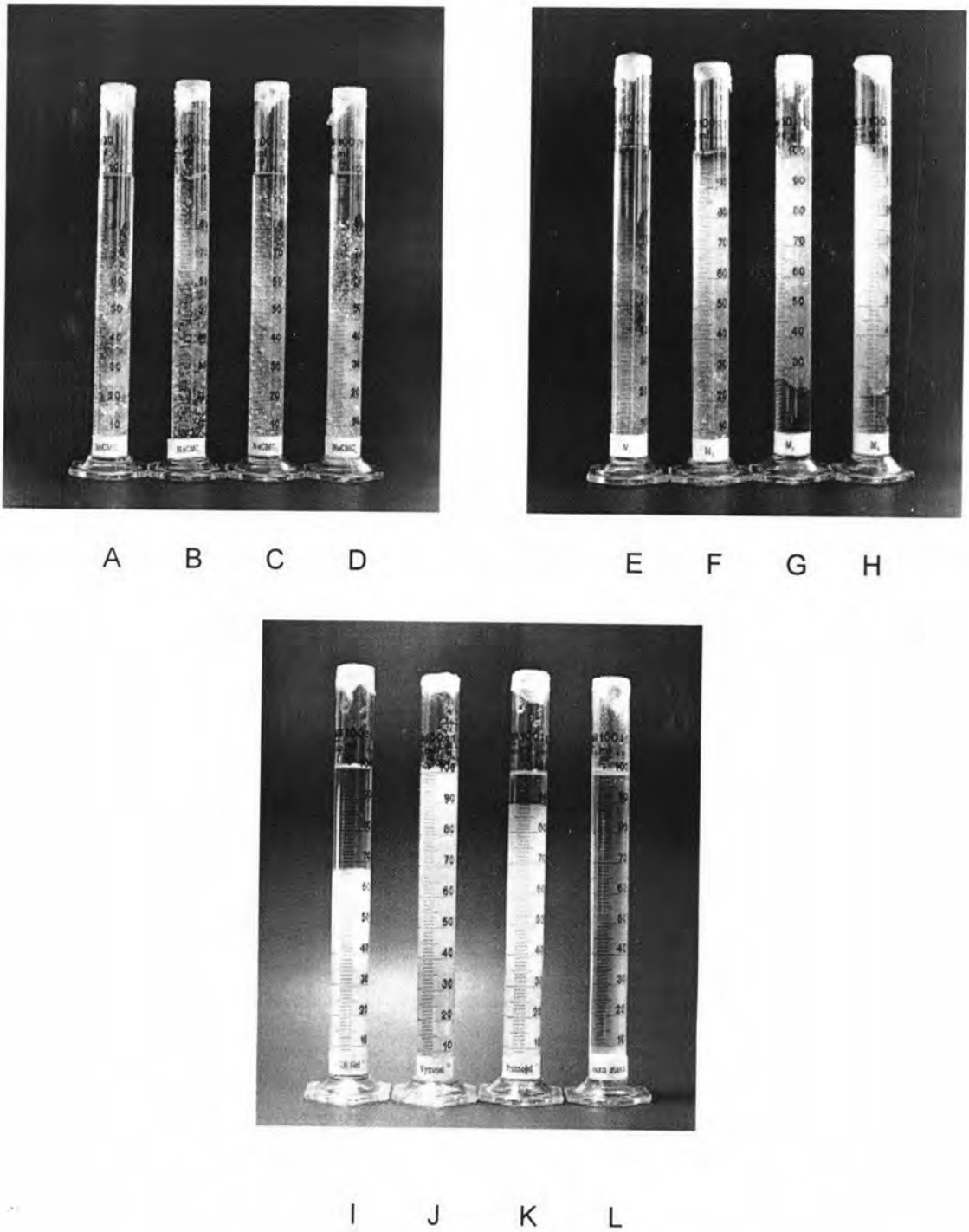


Figure 21 The sedimentation volume of disintegrants

A = NaCMC₁

E = M₁

I = Ac-di-sol[®]

B = NaCMC₂

F = M₂

J = Nymcel[®]

C = NaCMC₃

G = M₃

K = Primojel[®]

D = NaCMC₄

H = M₄

L = corn starch

4.4 Hydration Capacity

The hydrophilicity of disintegrant was expressed as a hydration capacity. The hydration capacity wherein water actually wet the material revealed about the same liquid-solid interactions or swelling power (Kornblum and Stoopak, 1973). The good disintegrant should be great ease to hydration. In this study the results of hydration capacity were corresponding to sedimentation volume. The results of hydration capacity of various disintegrants are summarized in Table 19. They were ranked as follows: Primojel[®] > Ac-di-sol[®] > corn starch. The statistical differences are illustrated in Table 49 and 50 (Appendix III). And the significantly difference ($p < 0.05$) was observed in the hydration capacity of Primojel[®], Ac-di-sol[®] and corn starch. Like the sedimentation volume, the hydration capacity of sodium carboxymethylcellulose, modified sodium carboxymethylcellulose and Nymcel could not be determined.

The hydration capacity of Primojel[®] and Ac-di-sol[®] were significantly higher than that of corn starch. This result showed the evidence of the superiority in the hydrophilicity of Primojel[®] and Ac-di-sol[®] over corn starch. The same trend was also found in the water uptake study. For Nymcel[®], sodium carboxymethylcellulose and modified sodium carboxymethylcellulose, the hydration capacity could not be determined because they partially dissolved in medium and formed clear gel. In this study, the procedure utilized was developed for materials that do not contain appreciable (over 25%) water-soluble constituents (Kornblum and Stoopak, 1973).

Table 19 The hydration capacity of disintegrants

Material	Hydration capacity* (ml/gm) \pm SD
NaCMC ₁	non-detectable
M ₁	non-detectable
NaCMC ₂	non-detectable
M ₂	non-detectable
NaCMC ₃	non-detectable
M ₃	non-detectable
NaCMC ₄	non-detectable
M ₄	non-detectable
Ac-di-sol [®]	13.84 \pm 0.42
Nymcel [®]	non-detectable
Primojel [®]	18.35 \pm 0.38
corn starch	1.80 \pm 0.13

* The mean of three determinations

The four physical parameters discussed may possible predict the relative usefulness and efficiency of new materials as disintegrant. The major emphasis apparently must be placed upon water uptake and swelling. Corn starch may be employed to establish a baseline for comparison of these properties with the new materials.

5. Evaluation of Disintegrating Property of Modified Sodium Carboxymethylcellulose Compared with Sodium Carboxymethylcellulose Used as Starting Materials and Commercial Disintegrants

The tablets prepared by direct compression using α -lactose monohydrate or dibasic calcium phosphate dihydrate as diluent and sodium

carboxymethylcellulose, modified sodium carboxymethylcellulose, Ac-di-sol[®], Nymcel[®], Primojel[®] or corn starch at concentration of 2%, 4% and 6% as disintegrant, compressed at three compressional forces (3000, 3500 and 4000 pounds) were observed for disintegrating property. The results of disintegration time of α -lactose monohydrate tablets containing various concentration of disintegrants at three compressional forces are shown in Table 20 and those of dibasic calcium phosphate dihydrate tablets are shown in Table 21.

5.1 α -Lactose Monohydrate Tablets

Since lactose was soluble in aqueous media, its behavior in the absence of disintegrant should be properly described as slow dissolution rather than disintegration. However, for sake of uniformity and for purposes of comparison, the term disintegration will be used throughout this paper to describe the behavior of the control tablets.

5.1.1 Disintegrating property of modified sodium carboxymethylcellulose

For any disintegrants, the disintegration time of lactose tablets range from less than 1 minute to more than 30 minutes. The blank tablet failed to disintegrate after 30 minutes of exposure. This could be clearly seen that lactose did not exhibit any disintegration property.

The lactose tablets containing various sodium carboxymethylcellulose had disintegration time about 1 minute to more than 30 minutes, which were considerably longer than any other disintegrants. The disintegration time of NaCMC₁, NaCMC₂, NaCMC₃ and NaCMC₄ were in the range of 18.44 to 25.34, 0.53 to more than 30.00, 13.08 to more than 30.00 and 28.74 to more than 30.00 minutes depending on the concentration employed, respectively. Among the various sodium carboxymethylcellulose, NaCMC₂ had the shortest disintegration time. This may be due to NaCMC₂

Table 20 Disintegration time of lactose tablets containing different disintegrants at various compressional forces

Disintegrant	Concentration (%w/w)	Disintegration time* (min) \pm SD		
		Compressional force (lb)		
		3000	3500	4000
blank	-	>30.00	>30.00	>30.00
NaCMC ₁	2	18.44 \pm 1.77	18.43 \pm 1.66	21.24 \pm 1.55
	4	21.63 \pm 0.46	20.49 \pm 0.41	23.38 \pm 1.34
	6	21.73 \pm 3.81	21.75 \pm 0.76	25.34 \pm 0.61
NaCMC ₂	2	3.55 \pm 1.93	1.65 \pm 0.53	0.53 \pm 0.02
	4	>30.00	>30.00	>30.00
	6	>30.00	>30.00	>30.00
NaCMC ₃	2	14.78 \pm 1.10	15.07 \pm 1.49	13.08 \pm 1.02
	4	30.00 \pm 1.22	30.00 \pm 0.87	29.09 \pm 1.83
	6	>30.00	>30.00	>30.00
NaCMC ₄	2	29.87 \pm 0.23	29.63 \pm 0.90	28.74 \pm 0.82
	4	>30.00	>30.00	>30.00
	6	>30.00	>30.00	>30.00
M ₁	2	0.65 \pm 0.04	0.67 \pm 0.04	0.73 \pm 0.04
	4	0.73 \pm 0.06	0.57 \pm 0.03	0.62 \pm 0.03
	6	3.71 \pm 1.83	0.81 \pm 0.11	0.79 \pm 0.07
M ₂	2	0.24 \pm 0.01	0.28 \pm 0.01	0.35 \pm 0.01
	4	0.25 \pm 0.00	0.27 \pm 0.01	0.31 \pm 0.01
	6	0.68 \pm 0.06	0.53 \pm 0.08	0.31 \pm 0.01
M ₃	2	0.39 \pm 0.02	0.30 \pm 0.01	0.26 \pm 0.01
	4	2.11 \pm 0.50	1.70 \pm 0.17	1.46 \pm 0.12
	6	4.04 \pm 0.39	4.12 \pm 0.61	6.21 \pm 0.91
M ₄	2	0.28 \pm 0.00	0.31 \pm 0.01	0.36 \pm 0.01
	4	0.71 \pm 0.03	0.56 \pm 0.03	0.45 \pm 0.02
	6	1.26 \pm 0.05	1.12 \pm 0.05	1.07 \pm 0.05

Table 20 (cont.)

Disintegrant	Concentration (%w/w)	Disintegration time* (min) \pm SD		
		Compressional force (lb)		
		3000	3500	4000
Ac-di-sol [®]	2	0.30 \pm 0.02	0.26 \pm 0.02	0.24 \pm 0.01
	4	0.46 \pm 0.02	0.45 \pm 0.01	0.41 \pm 0.02
	6	0.59 \pm 0.01	0.59 \pm 0.04	0.57 \pm 0.01
Nymcel [®]	2	0.24 \pm 0.01	0.20 \pm 0.02	0.21 \pm 0.01
	4	0.46 \pm 0.03	0.41 \pm 0.01	0.40 \pm 0.02
	6	0.84 \pm 0.01	0.75 \pm 0.04	0.65 \pm 0.04
Primojel [®]	2	0.28 \pm 0.01	0.28 \pm 0.00	0.31 \pm 0.01
	4	0.43 \pm 0.01	0.42 \pm 0.00	0.41 \pm 0.01
	6	0.54 \pm 0.01	0.52 \pm 0.01	0.51 \pm 0.02
corn starch	2	3.41 \pm 0.18	4.42 \pm 0.79	4.80 \pm 0.60
	4	1.47 \pm 0.17	2.18 \pm 0.49	1.96 \pm 0.38
	6	0.56 \pm 0.05	0.59 \pm 0.05	0.66 \pm 0.07
NaCMC ₃ + Na ₃ P ₃ O ₉ **	2	14.96 \pm 0.77	2.57 \pm 0.63	1.19 \pm 0.10
	4	28.59 \pm 0.97	29.72 \pm 0.55	29.33 \pm 0.82
	6	>30.00	>30.00	>30.00
M ₃ (no Na ₃ P ₃ O ₉)***	2	>30.00	>30.00	>30.00
	4	>30.00	>30.00	>30.00
	6	>30.00	>30.00	>30.00

* The mean of six determinations

** The physical mixture of NaCMC₃ and sodium trimetaphosphate

*** NaCMC₃ which treated with the same condition of cross-linking reaction but no added sodium trimetaphosphate

Table 21 Disintegration time of dibasic calcium phosphate dihydrate tablets containing different disintegrants at various compressional forces

Disintegrant	Concentration (%w/w)	Disintegration time* (min) ± SD		
		Compressional force (lb)		
		3000	3500	4000
blank	-	>30.00	>30.00	>30.00
NaCMC ₁	2	>30.00	>30.00	>30.00
	4	>30.00	>30.00	>30.00
	6	>30.00	>30.00	>30.00
NaCMC ₂	2	>30.00	>30.00	>30.00
	4	>30.00	>30.00	>30.00
	6	>30.00	>30.00	>30.00
NaCMC ₃	2	>30.00	>30.00	>30.00
	4	>30.00	>30.00	>30.00
	6	>30.00	>30.00	>30.00
NaCMC ₄	2	>30.00	>30.00	>30.00
	4	>30.00	>30.00	>30.00
	6	>30.00	>30.00	>30.00
M ₁	2	2.48 ± 7.17 (0.32 ± 0.05)	3.68 ± 3.45 (0.31 ± 0.03)	22.28 ± 7.63 (0.33 ± 0.02)
	4	5.02 ± 3.97 (0.25 ± 0.02)	4.65 ± 1.13 (0.32 ± 0.00)	6.76 ± 6.17 (0.35 ± 0.02)
	6	5.97 ± 3.97 (1.72 ± 0.26)	2.53 ± 1.04 (1.54 ± 0.26)	14.04 ± 3.11 (1.25 ± 0.13)
M ₂	2	3.46 ± 1.57 (0.27 ± 0.03)	7.54 ± 2.21 (0.26 ± 0.01)	0.36 ± 0.11 -
	4	0.68 ± 0.42	0.71 ± 0.15	1.15 ± 0.23
	6	0.43 ± 0.02	0.47 ± 0.01	0.54 ± 0.04
M ₃	2	3.06 ± 2.02 (0.35 ± 0.02)	1.95 ± 0.87 (0.41 ± 0.08)	3.64 ± 2.27 (0.39 ± 0.02)
	4	0.60 ± 0.19 (0.32 ± 0.02)	0.63 ± 0.15 (0.36 ± 0.03)	3.24 ± 0.96 (0.35 ± 0.02)
	6	0.76 ± 0.05	0.83 ± 0.11	0.95 ± 0.16
M ₄	2	6.02 ± 5.32 (0.22 ± 0.02)	5.47 ± 4.77 (0.23 ± 0.02)	12.77 ± 12.31 (0.25 ± 0.00)
	4	2.70 ± 3.14 (0.25 ± 0.01)	3.05 ± 3.14 (0.27 ± 0.01)	2.84 ± 3.10 (0.30 ± 0.02)
	6	2.79 ± 0.39 (0.31 ± 0.01)	0.57 ± 0.03 (0.33 ± 0.03)	2.08 ± 0.49 (0.36 ± 0.03)

Table 21 (cont.)

Disintegrant	Concentration (%w/w)	Disintegration time* (min) ± SD		
		Compressional force (lb)		
		3000	3500	4000
Ac-di-sol®	2	0.09 ± 0.01	0.10 ± 0.01	0.11 ± 0.01
	4	0.08 ± 0.00	0.09 ± 0.01	0.09 ± 0.00
	6	0.10 ± 0.01	0.10 ± 0.00	0.11 ± 0.01
Nyrncel®	2	0.19 ± 0.02	0.19 ± 0.02	0.22 ± 0.02
	4	0.16 ± 0.00	0.17 ± 0.00	0.18 ± 0.00
	6	0.16 ± 0.01	0.17 ± 0.01	0.19 ± 0.01
Primojel*	2	0.27 ± 0.01	0.26 ± 0.04	0.33 ± 0.04
	4	0.19 ± 0.03	1.34 ± 0.60	2.08 ± 0.74
	6	-	(0.22 ± 0.02)	(0.23 ± 0.02)
corn starch	2	0.17 ± 0.00	0.28 ± 0.01	0.20 ± 0.01
	4	>30.00	>30.00	>30.00
	6	>30.00	>30.00	>30.00
NaCMC ₃ + Na ₃ P ₃ O ₉ **	2	>30.00	>30.00	>30.00
	4	>30.00	>30.00	>30.00
	6	>30.00	>30.00	>30.00
M ₃ (no Na ₃ P ₃ O ₉)***	2	>30.00	>30.00	>30.00
	4	>30.00	>30.00	>30.00
	6	>30.00	>30.00	>30.00

* The mean of six determinations

** The physical mixture of NaCMC₃ and sodium trimetaphosphate

*** NaCMC₃ which treated with the same condition of cross-linking reaction but no added sodium trimetaphosphate

() The time that the tablet disintegrated completely but the residues still presented on the sieve

had the degree of substitution lower than that of the others sodium carboxymethylcellulose. Degree of substitution of NaCMC₂ was 0.63 and that of the others sodium carboxymethylcellulose was 0.65-0.75. It was corresponding to Shah et al's study which reported that the gums with a low degree of substitution together with a high degree of polymerization were excellent disintegrating agents (Shah et al., 1981). It can be stated that NaCMC₄ promoted tablet disintegration less than the others sodium carboxymethylcellulose because it had the highest viscosity that formed very viscous gel around the tablet, thus preventing water penetration into these tablets.

The disintegration time of modified sodium carboxymethylcellulose in lactose tablets was in the range of 0.24 to 6.21 minutes. These tablets showed modified sodium carboxymethylcellulose to be superior to sodium carboxymethylcellulose from a disintegration time standpoint. This may be caused by the modified sodium carboxymethylcellulose had a decreased water solubility, decreased gel formation, increased swelling and increased water uptake when compared with sodium carboxymethylcellulose used as the starting materials. When compared to Ac-di-sol[®], Nymcel[®] or Primojel[®], modified sodium carboxymethylcellulose was comparable to these disintegrants which gave the disintegration time of lactose tablet lower than 1 minute except these tablets containing M₃ at 4% concentration and M₁, M₃, M₄ at 6% concentration. However, the disintegration time of modified sodium carboxymethylcellulose was less than 7 minutes. It can be conclude that modified sodium carboxymethylcellulose in lactose tablet was comparable to Ac-di-sol[®], Nymcel[®] and Primojel[®] but M₃ was less effective, especially at high concentration. The lactose tablets containing corn starch had disintegration time in the range of 0.56 to 4.80 minutes. Thus, modified sodium carboxymethylcellulose was also comparable to corn starch. In the case of corn starch which mechanism of disintegration was due to capillary

action instead of swelling, the water penetrated rapidly along a capillary network. Also, erosion at the outer surfaces of lactose tablets due to the dissolving lactose caused the tablets to break apart. Therefore, the short disintegration time of lactose tablets with corn starch was obtained.

The disintegration time of the physical mixture of sodium carboxymethylcellulose and sodium trimetaphosphate ($\text{NaCMC}_3 + \text{Na}_3\text{P}_3\text{O}_9$) was in the range of 1.19 to more than 30 minutes. And that of M_3 which treated with the same condition of cross-linking reaction but no added sodium trimetaphosphate was more than 30 minutes. These results confirmed that the cross-linking reaction of sodium carboxymethylcellulose with sodium trimetaphosphate gave the substance which promoted disintegrating properties of tablets.

5.1.2 Effect of Concentration of Disintegrant on Disintegration Time

To studied the effect of concentration of disintegrant on disintegration time, the level of 2, 4 and 6% of any disintegrants were used. In all case, the increasing of concentration of disintegrants caused the longer disintegration time except the tablets containing corn starch showed the decreasing of disintegration time when its concentration increased.

The lower concentration of various sodium carboxymethylcellulose resulted in the faster disintegration time than the higher concentration. For instance, NaCMC_1 at 2% concentration had disintegration time in the range of 18.43 to 21.24 minutes. When the concentration was increased to 4%, the disintegration time of this was also increased between 20.49 and 23.38 minutes. In the same way, at 6% concentration, the disintegration time of NaCMC_1 was increased in the range of 21.73 to 25.30 minutes. When added NaCMC_2 , NaCMC_3 or NaCMC_4 at the concentration of 4% and 6% into the formulation of lactose tablets, these

materials were unable to make the tablets disintegrated within 30 minutes, except 4% of NaCMC₃ gave the disintegration time of lactose tablet about 30 minutes. Although tablets containing NaCMC₁ could be disintegrated within 30 minutes, it had a long disintegration time. These were due to the gelling of the tablet surface due to the dissolution of these materials in water. The amount of disintegrant increased, viscous gel also increased then disintegration time was delayed.

The outstanding difference between modified sodium carboxymethylcellulose and sodium carboxymethylcellulose was its ability to bring about rapid disintegration with relatively low concentration. For example, at 2% concentration of disintegrant, the disintegration time of M₁, M₂, M₃ and M₄ was in the range of 0.65-0.73, 0.24-0.35, 0.26-0.39 and 0.28-0.36 minute, respectively. Whereas that of NaCMC₁, NaCMC₂, NaCMC₃ and NaCMC₄ was in the range of 18.44-21.24, 0.53-3.55, 13.08-15.07 and 28.74-29.87 minutes, respectively. The lactose tablets using the modified sodium carboxymethylcellulose as a disintegrant exhibited longer disintegration time when concentration of disintegrant increased like sodium carboxymethylcellulose. For instance, the lactose tablets containing 2% of M₃ as a disintegrant had disintegration time between 0.26 and 0.39 minutes. At 4% concentration of M₃, the disintegration time was increased to 1.46-2.11 minutes. And the disintegration time was also increased to 4.04-6.21 minutes when the concentration of M₃ increased to 6%. Slow disintegration of tablets at high concentration of modified sodium carboxymethylcellulose may be due to the partially gel formation of modified sodium carboxymethylcellulose powders built up the barrier preventing penetration of water into the tablet matrix, however the gel formation of modified sodium carboxymethylcellulose was less than that of sodium carboxymethylcellulose.

Although Ac-di-sol[®], Nymcel[®] and Primojel[®] gave a rapid disintegration time of tablets (less than 1 minute), the time of disintegration

slightly increased when the concentration of disintegrants increased. The disintegration time of lactose tablets containing 2%, 4% and 6% concentration of Ac-di-sol[®] was 0.24-0.30, 0.41-0.46 and 0.57-0.59 minute, respectively. The lactose tablets with 2%, 4% and 6% of Nymcel[®] had disintegration time of 0.20-0.24, 0.40-0.46 and 0.65-0.84 minute, respectively. And the disintegration time of 2%, 4% and 6% of Primojel[®] in lactose tablets was 0.28-0.31, 0.41-0.43 and 0.51-0.54 minute, respectively. The result of the short disintegration time of water soluble system would depend upon the combine effect between dissolution of water soluble diluent and rapid water sorption of disintegrant.

It was shown that the lactose tablets containing corn starch had a short disintegration time (0.56 to 4.80 minutes) and the decreasing of disintegration time was influenced by the concentration of disintegrant. The shorter disintegration time was found when the concentration of corn starch increased. For example, at the compressional force of 3000 pounds, the disintegration time of lactose tablets containing 2% , 4% and 6% of corn starch were 3.41, 1.47 and 0.56 minutes, respectively. Commons et al. (1968) cited in Lowenthal (1972) observed in tolbutamide , aspirin, salicylamide and phenylbutazone tablets that the starch stained with iodine formed continuous chains along the channels between granules even at concentrations below those required to caused tablets to disintegrate. As percent of starch increased, thicker chains were formed, thus enlarging the pores and promoting disintegration. Patel and Hopponen (1966) cited in Lowenthal (1972) also stated that if starch grain contact was not continuous, disintegration time increased.

5.1.3 Effect of Compressional Force on Disintegration Time

The compressional force used was varied in 3000, 3500 and 4000 pounds. From Table 20, it can be concluded that the compressional

force appeared to have slightly affected the disintegration time. These tablets showed the small range in disintegration time at all compressional force used.

The disintegration time of lactose tablets containing NaCMC₁ was in the range of 18.44-21.73, 18.43-21.75 and 21.24-25.34 minutes when compressed these tablets at 3000, 3500 and 4000 pounds, respectively. At the compressional force of 3000, 3500 and 4000 pounds, the disintegration time of lactose tablets containing 2% concentration of NaCMC₂ was 3.55, 1.65 and 0.53 minutes, respectively, that of NaCMC₃ was 14.78, 15.07 and 13.08 minutes and finally, that of NaCMC₄ was 29.87, 29.63 and 28.74 minutes. When the concentration of NaCMC₂, NaCMC₃ and NaCMC₄ increased to 4% and 6%, the effect of compressional force on disintegration time was not observed because these tablets had the disintegration time more than 30 minutes, except the tablets containing 4% NaCMC₃ which gave the disintegration time almost equal at all compressional forces used (29.09-30.00 minutes).

The compressional force had also slightly affected on disintegration time of the lactose tablets containing modified sodium carboxymethylcellulose. The disintegration time of lactose tablets containing M₁ was in the range of 0.65-3.71, 0.67-0.81 and 0.62-0.79 minute at the compressional force of 3000, 3500 and 4000, respectively. When the compressional force increased from 3000 to 3500 and to 4000 pounds the disintegration time of lactose tablets with M₂ was in the range of 0.24-0.68, 0.27-0.53 and 0.31-0.35 minute and that of tablets with M₃ was 0.39-4.04, 0.30-4.12 and 0.26-6.21 minutes, respectively. For the lactose tablets containing M₄, the disintegration time was 0.28-1.26, 0.31-1.12 and 0.36-1.07 minutes at compressional force of 3000, 3500 and 4000 pounds, respectively.

Disintegration time of tablets containing Ac-di-sol[®], Nymcel[®] or Primojel[®] was slightly decreased when the compressional force

increased. The disintegration time of lactose tablets with Ac-di-sol[®] at compressional force of 3000, 3500 and 4000 pounds were in the range of 0.30-0.59, 0.26-0.59 and 0.24-0.57 minute, respectively and that of Nymcel[®] was 0.24-0.84, 0.20-0.75 and 0.21-0.65 minute and finally, that of Primojel[®] was 0.28-0.54, 0.28-0.52 and 0.31-0.51 minute. A somewhat similar insensitivity of disintegration time to compressional force was found by Miller et al. (1980) when studying the behavior of acetaminophen tablets containing Ac-di-sol[®] or Primojel[®]. They found that increasing compressional force had little effect on disintegration time. Vades et al. (1984) had studied the effect of compressional force on tablets containing cellulosic disintegrant. They found that two internally cross-linked sodium carboxymethylcellulose disintegrants were the most efficient and their efficiency increased with increasing compressional force.

The increasing of compressional force had also slightly affected to the disintegration time of lactose tablets containing corn starch. The compressional force increased, the disintegration time was increased. The disintegration time changed from 0.56-3.41 to 0.59-4.42 minutes when the compressional force increased from 3000 to 3500 pounds, and finally it was 0.66-4.80 minutes when these tablets was compressed at 4000 pounds. This might be the reduction of the pore size inhibiting water to penetrate into tablets so that disintegration time became longer. Previously, it has been shown by Levy et al. (1963) cited in Khan and Rooke (1976) that when tablets are prepared containing starch an increase in compressional pressure caused an increase in dissolution rate. It was suggested that fragmentation at high pressure was the reason.

5.2 Dibasic Calcium Phosphate Dihydrate Tablets

The aqueous solubility of formula can be used to explain the differences in the magnitude of effectiveness between the lactose formulation with disintegrant and the dibasic calcium phosphate dihydrate formulation

with disintegrant. Although the disintegrant significantly improved disintegration in both of these systems when compared with control formulation, the dibasic calcium phosphate dihydrate formulation exhibited a slightly faster disintegration time than their lactose counterparts. Since lactose was water soluble, it dissolved and formed a diffusion barrier layer of saturated lactose solution around the tablet. This diffusion layer may impede the availability of water to the disintegrant, reducing the rate of water entry. Dibasic calcium phosphate dihydrate was insoluble in water. Therefore, with the addition of a disintegrant, the matrix can be quickly broken up with no soluble diffusion layer present allowing the disintegrant to more readily pick up water and thus speed disintegration. The high solubility in formulation have a deleterious effect on superdisintegrant efficiency in wet granulated tablets. It appears that the high soluble ingredient may compete with the superdisintegrants for water, thus inhibiting disintegrant action (Johnson et al., 1991).

5.2.1 Disintegrating property of modified sodium carboxymethylcellulose

Disintegration time of the control formulation and the formulations containing various disintegrants in dibasic calcium phosphate dihydrate system were similar to those of α -lactose monohydrate system except tablets containing corn starch. In dibasic calcium phosphate dihydrate tablets, corn starch showed to be inferior to the lactose tablets, that was these tablets failed to disintegrate after 30 minutes exposure. Like the tablets containing various sodium carboxymethylcellulose and the control formulation, these tablets gave disintegration time more than 30 minutes.

It is evidenced that the modified sodium carboxymethylcellulose are more efficient than sodium carboxymethylcellulose in the lactose system (Table 20), while also being more efficient in the dibasic calcium phosphate dihydrate formulations. From

Table 21, the disintegration time of 2% M_1 at 3000 pounds was 2.48 (0.32), that means these tablets disintegrated completely within 0.32 minute and the residues still presented on the sieve. At the time of 2.48 minutes, the residues was absented. The disintegration time of dibasic calcium phosphate dihydrate tablets containing modified sodium carboxymethylcellulose was in the range of 0.36 to 22.28 minutes. Really, these tablets disintegrated within 1.72 minutes but the residues of tablet still presented on the sieve and they absented at the time of 22.28 minutes, so the disintegration time was very long. It can be explained that when the tablet contacted with water the gel formation of modified sodium carboxymethylcellulose may be combined dibasic calcium phosphate dihydrate particles together to enlarge particles, then it still presented on the sieve.

Among the four of modified sodium carboxymethylcellulose as tablet disintegrants, M_3 showed the shortest disintegration time, while M_1 showed the longest disintegration time. Disintegration time of tablets containing M_3 was in the range of 0.60 to 3.64 minutes and that of M_1 was between 2.48 and 22.28 minutes. These tablets disintegrated slower than the tablets containing Ac-di-sol[®], Nymcel[®] or Primojel[®]. Therefore it can be concluded that modified sodium carboxymethylcellulose was less effective than Ac-di-sol[®], Nymcel[®] and Primojel[®] in insoluble system.

The disintegration time of the physical mixture of sodium carboxymethylcellulose and sodium trimetaphosphate ($\text{NaCMC}_3 + \text{Na}_3\text{P}_3\text{O}_9$) was more than 30 minutes. And that of M_3 which treated with the same condition of cross-linking reaction but no added sodium trimetaphosphate was also more than 30 minutes. These results confirmed that the cross-linking reaction of sodium carboxymethylcellulose with sodium trimetaphosphate gave the substance which promoted the disintegration of tablets.

In dibasic calcium phosphate dihydrate system, the tablets containing Ac-di-sol[®], Nymcel[®] or Primojel[®] disintegrated slightly faster than in lactose system. The disintegration time of dibasic calcium phosphate dihydrate tablets containing Ac-di-sol[®], Nymcel[®] and Primojel[®] were 0.08-0.11, 0.16-0.22 and 0.17-2.08 minutes, respectively. While the lactose tablets with Ac-di-sol[®], Nymcel[®] and Primojel[®] had the disintegration time in the range of 0.24-0.59, 0.20-0.84 and 0.28-0.54 minute, respectively. It can be explained that the solubility of the major component in a tablet formulation affected both the rate and the mechanism of tablet disintegration. Water-soluble materials tend to dissolve rather than disintegrate, while insoluble materials will produce a rapidly disintegrating tablet if an appropriate amount of disintegrant was included in the formulation (Johnson et al., 1991). Bhatia et al. (1978) and Paronen et al. (1985) cited in Johnson (1991) showed that superdisintegrants had a much greater effect on disintegration time in an insoluble system than in a soluble or partially soluble system. Graf et al. (1982) cited in Visavarungroj and Remon (1990) stated that the swelling disintegrants retarded water penetration as the solubility of the other tablet ingredients increased, thus prolonging the disintegration time. The swelling particles of these disintegrants partially filled the void of lactose tablets and thus water could not easily penetrate into the tablets. An additional retarding effect can be expected because of the dissolved lactose making the penetrating water more viscous.

Corn starch was unable to make the dibasic calcium phosphate dihydrate tablets disintegrated within 30 minutes at all concentration and compression forces. These results demonstrated the poor disintegrating character of corn starch in these formulas. Corn starch did not swell in water and its mechanism of disintegration was based on water penetration due to capillary action, which developed insufficient internal pressure to induce complete tablet disintegration.

5.2.2 Effect of Concentration of Disintegrant on Disintegration Time

The concentration of disintegrant had slightly effect to the disintegration time of dibasic calcium phosphate dihydrate tablets. For these tablets containing various sodium carboxymethylcellulose and corn starch, there was no difference in disintegration time for the tablets using different concentrations of these disintegrants because these tablets failed to disintegrated within 30 minutes.

The disintegration time of dibasic calcium phosphate dihydrate tablets containing M_1 at 2 %, 4% and 6% concentration were in the range of 2.48-22.28, 5.02-6.76 and 2.53-14.04 minutes, respectively. For these tablets with M_2 at the concentration of 2%, 4% and 6% had the disintegration time between 0.36-7.54, 0.68-1.15 and 0.43-0.54 minutes, respectively. The tablets containing M_3 as a disintegrant had the disintegration of 1.95-3.64, 0.60-3.24 and 0.76-0.95 minutes when the concentration of disintegrant was 2%, 4% and 6%, respectively. Finally, the disintegration time of dibasic calcium phosphate dihydrate tablets containing 2% concentration of M_4 was in the range of 5.47-12.77 minutes. When the concentration of M_4 increased to 4%, the disintegration time was slightly increased to 2.70-3.05 minutes. At 6% concentration of M_4 , the disintegration time was 0.57-2.79 minutes. It can be seen that the concentration of various modified sodium carboxymethylcellulose had slightly effect to the disintegration time of dibasic calcium phosphate dihydrate tablets.

For the tablets containing Ac-di-sol[®], Nymcel[®] or Primojel[®], the concentration of disintegrant had also slightly effect to the disintegration time of tablets like that of modified sodium carboxymethylcellulose. The disintegration time of dibasic calcium phosphate dihydrate tablets with Ac-di-sol[®] at 2%, 4% and 6% concentration was 0.09-0.11, 0.08-0.09 and 0.10-0.11 minute, respectively. And that of Nymcel[®] was

0.19-0.22, 0.16-0.18 and 0.16-0.19 minute when the concentration of Nymcel[®] was 2%, 4% and 6%, respectively. The concentration of Primojel[®] at 2%, 4% and 6% made the dibasic calcium phosphate dihydrate tablets disintegrated at the time of 0.26-0.33, 0.19-2.08 and 0.17-0.28 minutes, respectively.

5.2.3 Effect of Compressional Force on Disintegration Time

In the case of sodium carboxymethylcellulose and corn starch, the disintegration time was more than 30 minutes at all compressional force. The disintegration time was not significant difference for the tablets formulated with sodium carboxymethylcellulose at various viscosity grade.

The compressional force had slightly influence on the disintegration time of dibasic calcium phosphate dihydrate tablets containing modified sodium carboxymethylcellulose. The compressional force increased the disintegration time was slightly increased. The disintegration time of tablets with M₁ was 2.48-5.97, 2.53-4.65 and 6.76-22.28 minutes when these tablets was compressed at 3000, 3500 and 4000 pounds, respectively. The dibasic calcium phosphate dihydrate tablets containing M₂ disintegrated at the time of 0.43-3.46, 0.47-7.54 and 0.36-1.15 minutes when the compressional force was 3000, 3500 and 4000 pounds, respectively. When the compressional force increased from 3000 to 3500 and to 4000 pounds the disintegration time of dibasic calcium phosphate dihydrate tablets with M₃ was also slightly increased in the range of 0.60-3.06, 0.83-1.95 and 0.95-3.64 minutes, respectively and that of M₄ was 2.70-6.02, 0.57-5.47 and 2.08-12.77 minutes.

The disintegration time of tablets containing Ac-di-sol[®] at the compressional force of 3000, 3500 and 4000 pounds was 0.08-0.10, 0.09-0.10 and 0.09-0.11 minute, respectively, that of Nymcel[®] was 0.16-0.19, 0.17-

0.19 and 0.18-0.22 minute and finally, that of Primojel[®] was 0.17-0.27, 0.26-1.34 and 0.20-2.08 minutes. It can be seen that, the difference in compressional force for dibasic calcium phosphate dihydrate tablets containing Ac-di-sol[®], Nymcel[®] or Primojel[®] did not reveal any influence on their disintegration time.

6. Evaluation of Modified Sodium Carboxymethylcellulose as Tablet Disintegrant in Paracetamol Tablets

It is generally accepted that disintegration is a necessary step in overall availability of a drug from a compressed tablet, disintegration time cannot be assumed to provide an accurate indication of bioavailability but may instead find greater application in initial formulation work and as an indicator of any batch-to-batch variation. Similarly, it has been shown that measurement of disintegration time may provide neither a quantitative nor a qualitative indication of the dissolution rates of tablets. In this study, the examination of disintegrants to determine their effect on disintegration time and dissolution profiles of tablets made from the analgesic, paracetamol were performed.

From the all of modified sodium carboxymethylcellulose in this study, M₄ was selected for evaluation of disintegration property in paracetamol tablets because it showed the highest swelling, although the water uptake of M₄ was inferior to that of M₂ and the disintegration property in soluble and insoluble system was comparable to the others modified sodium carboxymethylcellulose. And NaCMC₄ was used to compared with M₄ as the starting material. Paracetamol was employed as a model drug. The reason of selecting paracetamol as a model drug for evaluated the disintegrants because it was a poorly soluble drug and worldwide used as analgesic.

Paracetamol tablets were prepared by wet granulation. And the disintegrant was incorporated between two phases (intragranular and extragranular). The formulation and method of preparation has been described in the previous section (Table 5 in Chapter II) These tablets were evaluated for their physical properties as follows : weight variation, thickness, hardness, friability, disintegration time and dissolution.

6.1 Weight variation, Thickness, Hardness and Friability

The average values and standard deviations of weight, thickness and hardness including friability of paracetamol tablets are illustrated in Table 22. In all formulations, weight variation and standard deviation (1%) were complied with USP requirement. The thickness for each

Table 22 Physical properties of Paracetamol tablets with 4% disintegrants

Disintegrant	Physical properties				
	weight ^(a) (mg) ± SD	thickness ^(b) (mm) ± SD	hardness ^(b) (kp) ± SD	friability (%)	disintegration time ^(c) (min) ± SD
NaCMC ₄	625.95 ± 0.66	4.060 ± 0.029	6.5 ± 0.5	0.64	>30:00
M ₄	625.45 ± 0.52	4.158 ± 0.016	5.9 ± 0.2	0.66	11.66 ± 0.36
Ac-di-sol [®]	625.70 ± 0.70	4.140 ± 0.015	6.0 ± 0.3	0.90	1.14 ± 0.13
Nymcel [®]	622.35 ± 0.36	4.112 ± 0.014	5.8 ± 0.3	0.99	1.55 ± 0.04
Primojel [®]	628.50 ± 0.22	4.196 ± 0.013	5.9 ± 0.3	0.94	1.28 ± 0.03
corn starch	628.10 ± 0.69	3.898 ± 0.021	6.5 ± 0.7	0.76	8.49 ± 1.83
blank	625.90 ± 0.98	4.161 ± 0.018	5.6 ± 0.2	0.98	>30:00

(a) The mean of twenty determinations

(b) The mean of ten determinations

(c) The mean of six determinations

formulation was in the range of 3.898-4.196 mm and standard deviation was not more than 0.03. The hardness of tablets was in the range of 6 ± 1 kp. And the friability of tablets was in the acceptable limit (not more than 1%) but it was extremely poor for Ac-di-sol[®], Nymcel[®], Primojel[®] and blank tablets.

6.2 Disintegration time

The results of disintegration time of paracetamol tablets containing various disintegrants are shown in Table 22 and Figure 22. Tablets containing Ac-di-sol[®], Nymcel[®] or Primojel[®] shown the short disintegration time within a few minutes, followed by corn starch and M_4 . For paracetamol tablets with $NaCMC_4$ and the control tablets (no disintegrant), the disintegration time were not within the acceptable limit of USP standard, that was disintegration time more than 30 minutes. The statistical differences ($p < 0.05$) are shown in Table 51 and 52 (Appendix III). The M_4 was clearly more effective than $NaCMC_4$ as a disintegrant in paracetamol tablets, however it was not as effective as the strongly swelling disintegrants: Ac-di-sol[®], Nymcel[®] and Primojel[®]. The possible explanations for shorter disintegration time of tablets containing M_4 compared to tablets containing $NaCMC_4$ are high swellability, high water uptake and low tendency to gelling of M_4 . When compared to corn starch, M_4 promoted the disintegration of paracetamol tablets less than corn starch. It can be noticed that corn starch promoted the disintegration of paracetamol tablets more than dibasic calcium phosphate dihydrate tablets in spite of they were also insoluble system. It can be explained that the short disintegration time of paracetamol tablets with corn starch may be due to the formulation of paracetamol tablets composed of lactose which was soluble in water. The dissolving lactose caused the tablets to break apart, so the short disintegration time was obtained.

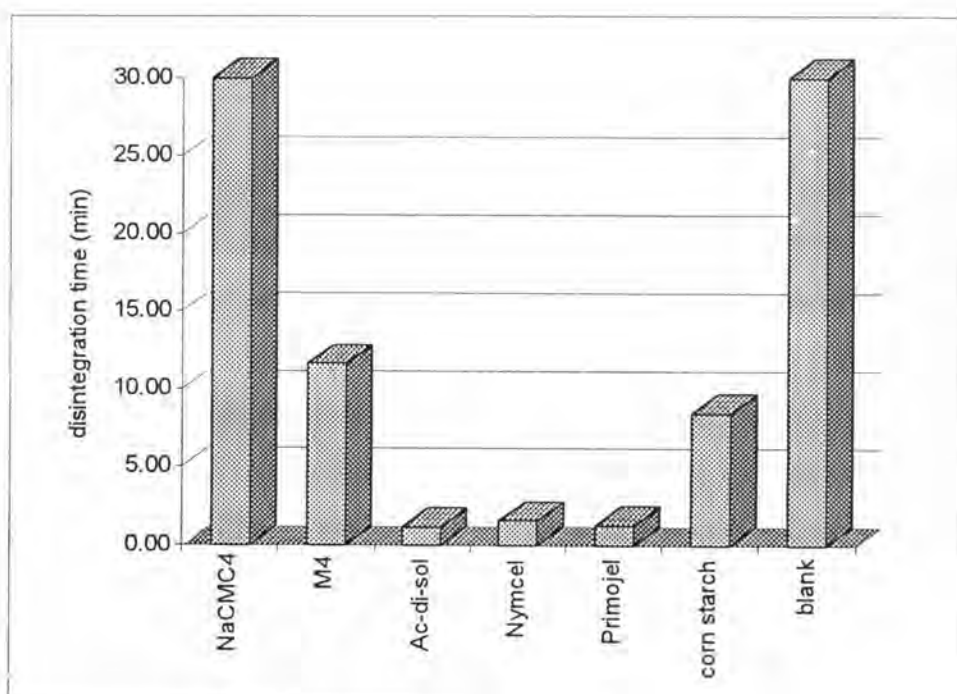


Figure 22 The disintegration time of paracetamol tablets containing various disintegrants

The penetration of water was a prerequisite for the disintegration of a tablet because it activated the mechanism which lead to disintegration (Van Kamp et al., 1986; Caramella et al., 1986 cited in Pesonen, Paronen and Ketolainen 1989). No direct correlation between the instant water penetration rate and the disintegration time was observed. Water penetration rate of M₄ was comparable to NaCMC₄ but the disintegration time of M₄ was faster than NaCMC₄.

6.3 Dissolution

To ascertain the overall acceptability of a new disintegrant, it must be shown that no interference with the dissolution behavior of the drug from the tablet is involved (Kornblum and Stoopak, 1973). To investigate this parameter for M₄, the tablets were formulated using paracetamol as a model drug. In this dissolution study, M₄ was again compared to sodium

carboxymethylcellulose, Ac-di-sol[®], Nymcel[®], Primojel[®], corn starch and blank tablets.

The dissolution data of paracetamol tablets containing various disintegrants in phosphate buffer pH 5.8 are presented in Table 23 and illustrated in Figure 23. And the statistical data are shown in Table 53 and 54 (Appendix III). The amount of paracetamol was released from the tablet containing NaCMC₄ and the blank tablet were significantly lower than the that of the others disintegrant.

Table 23 The dissolution of paracetamol tablets containing various disintegrants

Time (min)	Drug release* (%)						
	NaCMC ₄	M ₄	Ac-di-sol [®]	Nymcel [®]	Primojel [®]	corn starch	blank
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	1.03	19.23	33.09	20.30	29.64	3.06	1.23
2	1.49	36.49	65.84	50.60	68.88	8.13	1.70
5	2.36	69.01	92.35	83.03	97.04	31.73	3.96
10	3.46	98.20	101.08	93.72	99.81	65.15	7.68
15	4.64	102.27	101.64	94.01	100.07	88.98	11.24
20	6.03	101.60	100.84	94.02	99.14	96.46	14.90
25	6.89	101.71	100.75	93.36	98.43	98.14	18.26
30	7.86	100.53	100.36	92.60	97.95	98.05	21.49

* The mean of three determinations

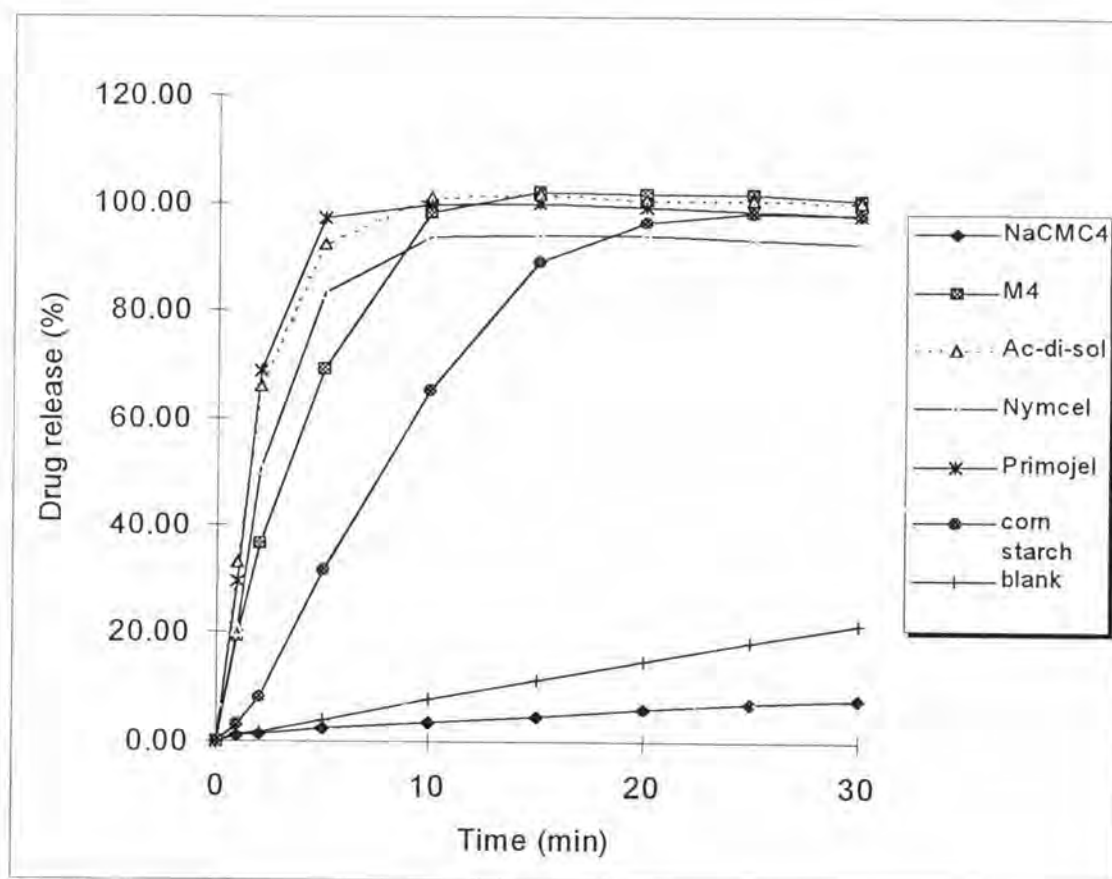


Figure 23 The dissolution profile of paracetamol tablets containing various disintegrants

The data shown in Table 22 summarized that some disintegrating agents gave a short disintegration time such as Ac-di-sol[®], Primojel[®] and Nymcel[®], consequently the fast dissolution of drug was obtained (Table 23). Ac-di-sol[®] and Primojel[®] lead to a fast liberation of paracetamol (within 10 minutes). M₄ gave the disintegration time of paracetamol tablets longer than corn starch but the dissolution rate of M₄ was higher than corn starch. In the case of NaCMC₄ which retarded the disintegration of tablets, it could be noticed that the amount of paracetamol dissolved less than that of control tablets. It could be explained that NaCMC₄ partially dissolved in medium and formed gelling barrier to prevent drug dissolved. At 30 minutes interval, the amounts of paracetamol dissolved were 100.53 % , 100.36 % , 98.05 % , 97.95 % , 92.60 % , 21.49 % and 7.86 % in

tablets containing M_4 , Ac-di-sol[®], corn starch, Primojel[®], Nymcel[®], no disintegrant and NaCMC₄, respectively.

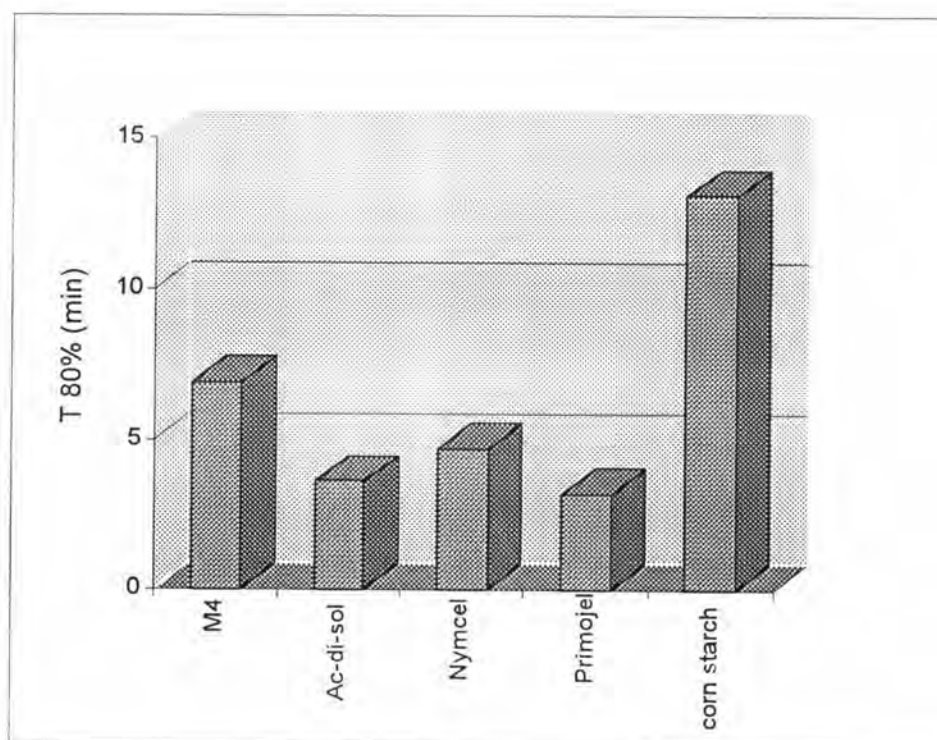
The results of disintegration and dissolution of paracetamol tablets without disintegrating agent showed that the disintegration time was very long and the dissolution was very low, therefore a disintegrant was necessary.

According to Figure 23, the dissolution profile of paracetamol tablets prepared from various disintegrants were seem not different, except NaCMC₄ and the control formulation. Dissolution rates of paracetamol tablets with M_4 , Ac-di-sol[®], Nymcel[®], Primojel[®] and corn starch were complied with the USP requirement (limit more than 80% of labeled amount dissolved within 30 minutes) but NaCMC₄ and the control formulation were not (exhibited the release of drug lower than the standard limit).

The amount of paracetamol dissolved from tablets containing various disintegrants was calculated. The $T_{80\%}$ values (the times at 80% drug released), in minutes, were ranked as in the following: Primojel[®] < Ac-di-sol[®] < Nymcel[®] < M_4 < corn starch (Table 24 and Figure 24). For NaCMC₄ and the control formulation, the release of paracetamol was less than 80% labeled amount.

Table 24 $T_{80\%}$ of paracetamol tablets containing various disintegrants

Disintegrant	$T_{80\%}$ (min)
M ₄	6.90
Ac-di-sol [®]	3.60
Nymcel [®]	4.70
Primojel [®]	3.18
corn starch	13.10

**Figure 24** Comparison $T_{80\%}$ of paracetamol tablets containing various disintegrants