CHAPTER III

PRELIMINARY INVESTIGATION ON DISINTEGRATING PROPERTIES OF CARBOXYMETHYL STARCH PRODUCES FROM VARIOUS NATIVE STARCHES

Starch, is at first, used as tablet disintegrant in native form without modification. In the past 30 years, there were incessantly developments of high efficiency disintegrant from native starches and other natural sources. The first successful attempt to improve the disintegration efficiency of native starch has been the development of a chemically modified potato starch which strongly increases swelling properties. This product, sodium carboxymethyl starch (sodium starch glycolate) was marketed in 1965 under the name Primojel^{R} and Explotab^{R}. Sodium starch glycolate is now widely used as tablet disintegrant, and is effective in concentrations as low as 2-4% (Bolhius, et al.,1984).

Nasipuri and Omotosho (1985) have investigated the effects of treating cassava starch (Tapioca starch) with sodium lauryl sulfate and polysorbate 80 and the method of incorporating the treated and plain starch as disintegrant on the physical properties of sulphadiazine tablets. Disintegration and dissolution rates were faster with starch in which surfactant was incorporated in dry state than with starch treated with solution of surfactant. Polysorbate 80 treated starch exhibited a better dissolution profile than sodium lauryl sulfate treated starch.

Crosslinked gum acacia has been investigated as tablet disintegrant by Trivedi, et al. (1986). They have prepared crosslinked gum acacia and evaluated as a tablet disintegrant. They found that crosslinked gum acacia brought about rapid disintegration as compared to corn starch. The increase in the percentage of the disintegrant from 2.5% to 7.0% reduces the disintegration time in all cases.

Furthermore, there were a number of reports which attempted to derive a starch from natural source to use as tablet disintegrant. Akande, et al. (1991) have investigated the starch obtained from Pearl Millet as a binder and disintegrant for compressed tablets.

Visavarungroj and Remon (1991) have investigated hydroxypropyl starch and pregelatinized hydroxypropyl starch as disintegrant and binder in tablet formulation. The study indicated that pregelatinized hydroxypropyl starch showed some good disintegrating properties and could be used as a binder in wet granulation.

Purpose of the study

The scope of the study in this part is to explore what sorts of the native starches which were available locally suitable for modification to be a new disintegrant which is more effective than the natural ones.

The selected native starches used in this study were commonly cultivated in Thailand : Corn starch, Rice starch, Glutinous rice starch, Wheat starch, Arrow root starch and Tapioca starch (the scanning electron micrographs of these starches are showed in Figure 4-9).

The method of modification was carboxymethyl substitution reaction. The reason to select this kind of modification was that the carboxymethyl starch is hydrophilic with strongly increased capillary property and increased swelling property which are the mechanisms of tablet disintegration (Bolhius, Kamp and Lerk, 1984 ; Shangraw, Mitrevej and Shah, 1980). In addition, the previous studies showed it breakthroughed to use carboxymethyl starch which was modified from potato starch as highly effective disintegrant. (Jaminet, Delattre and Delporte, 1969; Mendell, 1974 ; Khan and Rhodes, 1975 ; Bolhius, Smallenbroke and Lerk, 1981 ;Lerk, et al.,1982)

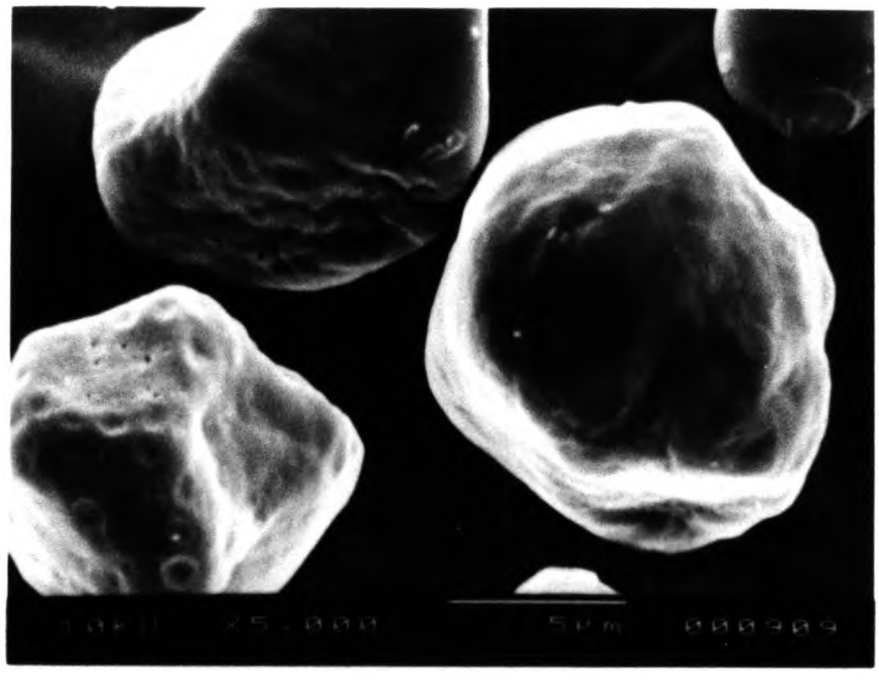

Figure 4 Scanning Electron Micrograph of Corn Starch, 5000x

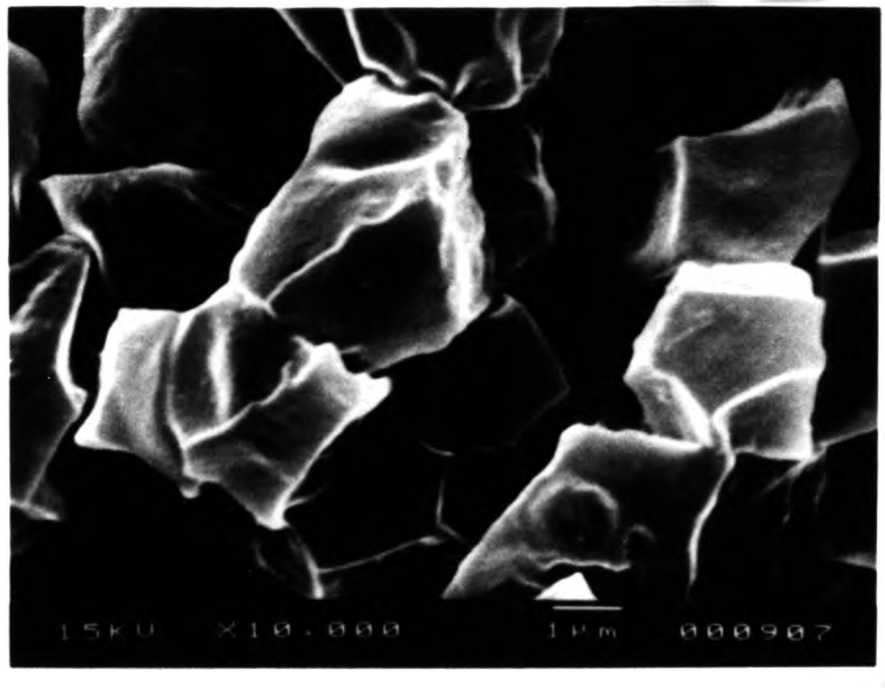

Figure 5 Scanning Electron Micrograph of Rice Starch, 5000x

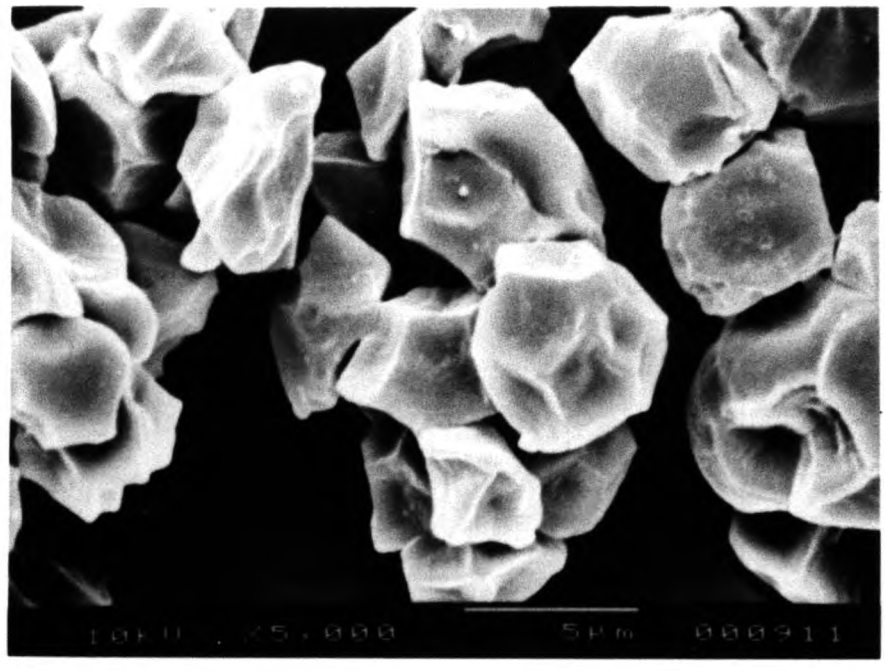

Figure 6 Scanning Electron Micrograph of Glutinous Rice Starch, 5000x

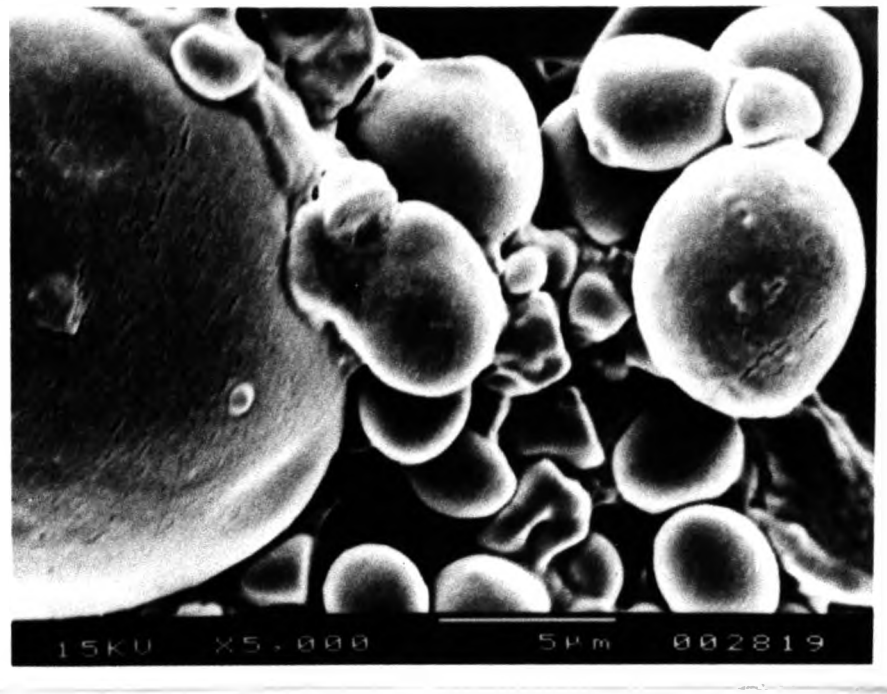

Figure 7 Scanning Electron Micrograph of Wheat Starch, 5000x

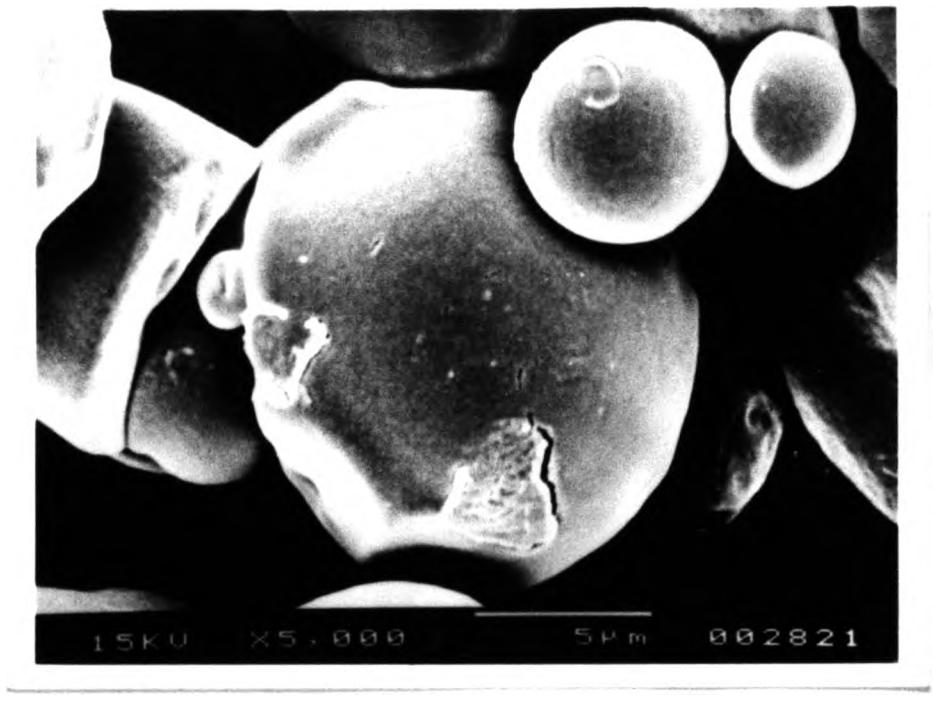

Figure 8 Scanning Electron Micrograph of Arrow Root Starch, 5000x

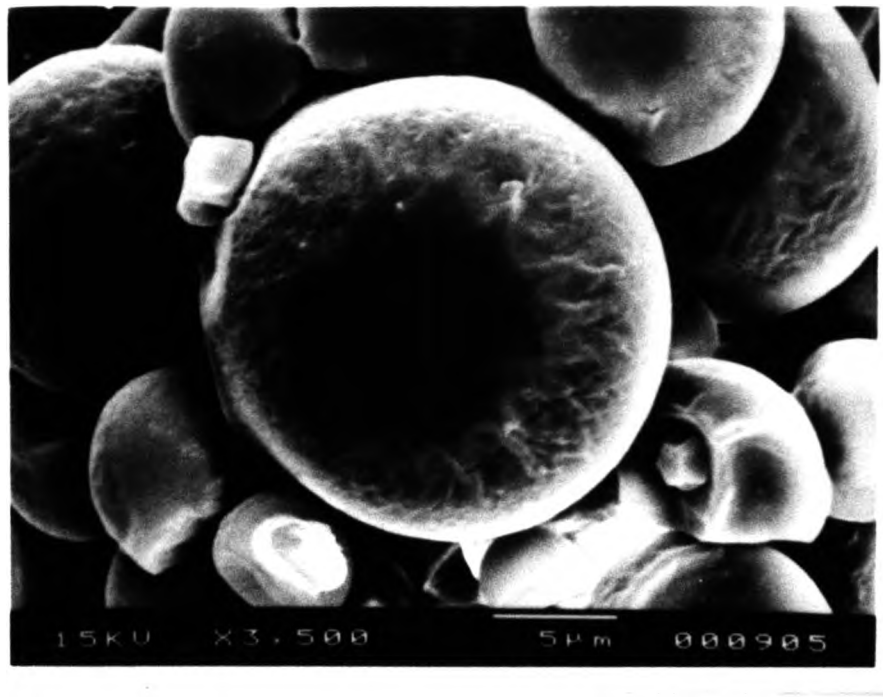

Figure 9 Scanning Electron Micrograph of Tapioca Starch, 5000x

Dicalcium phosphate and lactose were used as models of slightly soluble and soluble tablet systems respectively to test the disintegrating properties of the modified starches produced in comparison to commercial disintegrants. Furthermore, erythromycin stearate was also employed as a testing model. The reason of selecting erythromycin stearate as a model for disintegration study was its hydrophobic property and its difficulty to disintegrate when it was compressed in the tablet dosage form.

Materials and Methods

Materials :

Corn starch	(Mc.Garrett. Peter Rich & Co., Holland)
Rice starch	(Thai Better Food, Thailand)
Glutinous rice starch	(Thai Better Food, Thailand)
Wheat starch	(Leam Tong Sahakarn, Thailand)
Arrow root starch	(Chai Charoen, Thailand)
Tapioca starch	(Nguan Soon, Thailand)
Chloroacetic acid	(Sigma Chem. Co., USA, Lot. No. 111 Ho 240)
Methanol	(BHD Lab., England, Lot. No. 226 K 17948870)
Sodium hydroxide	(Eka Nobel, Sweden)
Acetic acid	(Riedel-de Haen, Germany, Lot. No.7313)
Dicalcium phosphate	(Mendell Co.Inc.,USA.Lot. No. K 27 A)
Lactose direct compressed	(The Lactose Company of New Zealand, Lot. No. 203114)
Erythromycin stearate	(GP.Lot. No. EST 103/93)
Magnesium stearate	(Peter Greven Fett. Chemie, Gmbtl & Co, Lot.No. CU 1952)

Explotab® (Mendell, NY, USA, Lot. No. E4222)

Primojel® (AVEBE, Holland)

Polyplasdone® XL (GAF, Singapore Pte, Ltd., Singapore)

Ac-Di-Sol® (FMC Corporation, USA, Lot. No. T 934)

Avicel® PH 101 (Asahi Chem. Industry, Japan)

Methods.

1. Preparation of Carboxymethyl starch.

The method of preparation were modified from Filbert's method(1952). Weighed 133 parts of methanol and 17.5 parts of chloroacetie acid, mixed thoroughly, and heated to 50 °C. Then 204 parts of finely divided starch were added with continuous mixing, followed by 30.5 parts of flake 97% sodium hydroxide dissolved in 68 parts of water. The reaction was held at 50° C for 1 hour with maintainance of good agitation, and then neutralized with acetic acid. After removal of the mother liquor, the product was washed several times with 80% methanol and finally with 100% of methanol. Dry the product by suspending in absolute alcohol and spraying into the hot coating pan. Collected the dried powder and screened through 80 mesh sieve.

2. Preparation of dicalcuim phosphate and lactose tablets

Experimental formulation of dicalcuim phosphate tablets was as follows:

Rx	Dicalcium phosphate	500 mg
	Disintegrant	5%
	Magnesium stearate	2.5 mg

Experimental formulation of lactose tablets was as follows :

Rx	Lactose direct comparessed	300 mg
	Disintegrant	5%
	Magnesium stearate	3.0 mg

The tablets were compressed by direct compression method on a single punch tablet machine, Yiuhang Engineering Model A, series 6, using flat face, 11/32 inches punches. The hardness of tablets were adjusted to about 4-6 kp for dicalcium phosphate tablets and 2-4 kp for lactose tablets.

3. Preparation of Erythromycin stearate tablets.

The experimental formulation of erythromycin stearate tablets was as follows :

R_X	Erythromycin stearate equivalent to	250 mg
	Lactose powder	150 mg
	PVP 30 K (10% in alcohol)	80 mg
	Disintegrant	10 mg
	Magnesium stearate	3 mg
	Aerosil^R	6 mg

The drug and diluents employed in each formulation were passed individually through a 40 mesh screen to break agglomerate. All ingredients except PVP 30K were weighed and mixed thoroughly by motar and pestle for about 3 min. The mixture was kneaded into damp mass with binding agent for 3 minutes. The binding agent was 10% PVP 30K solution in absolute alcohol. The damp mass was passed through a 16 mesh screen. The granules were tray dried in a drying oven for one hour at 50 °C. The dried granules were again passed through a 20 mesh screen. The tablets were compressed on single punch tablet machine, Yiuhang Engineering, model A, series 6, using flat face, 20/32 inches punch. The hardness of tablet were maintained about 4-6 kp.

4. Evaluation of Tablets

4.1) Hardness of Tablets

Five tablets were randomly selected and subjected to a hardness tester, Schleuniger-2E, model 2E/205. The mean and standard deviation were calculated.

4.2) Disintegration times of tablets

The disintegration times of tablets were determined in deionized water using Hanson Research Tablet Disintegration Tester, model 64-700-156, series No. 1529-17, USA. The mean of six determinations for each batch was calcutated.

4.3) Dissolution study

Only erythromycin stearate tablet was tested for dissolution characteristics. The dissolution studies were conducted by using USP dissolution type I method (Hanson Research SR2, USA). Nine hundred milliliters of distilled water was used as dissolution medium, which was maintained at 37°C. The basket containing one tablet was rotated at the speed of 100 rpm. Five- milliliters samples were withdrawn by a syringe at various time intervals. The absorbances of sample were determined by ultraviolet spectrophotometer (Hitachi spectrophotometer, model 150-20, serial No. 5914-30) at the maximum wavelength of 225.1 nm. Erythromycin stearate dissolved at various time intervals were calculated from the absorbance-concentration curve. To maintain a constant volume of dissolution medium, five milliliters of fresh medium was replaced after removal of each sample.

Results and Discussion

Disintegration time studies of dicalcium phosphate and lactose tablets

The disintegration times of dicalcium phosphate tablets containing 5% of various disintegrants are shown in Table 3. The dicalcuim phosphate tablets without disintegrant showed a poor disintegration (longer than 30 minutes) due to its insoluble property and hydrophobicity. When various types of starch (both of the native starches and the modified carboxymethyl starches) were used as tablet disintegrants, the disintegration times of tablet were markedly decrease due to the capillary action of the starches and swelling property of the starches (Curlin, 1955). Among the six native starches as tablet disintegrants, tapioca starch showed the best disintegrating properties.

The modified carboxymethyl starches showed the better disintegrating property than the blank tablet and corresponding native starches. This could be attributed to the hydrophilicity of carboxymethyl starch.However, it is not complete water soluble when exposed to water, the modified starch grains swell without losing their integrity and cause tablet disintegrated (Shangraw, Mitrevej and Shah, 1980).

Among the six modified carboxymethyl starches, tapioca starch glycolate and glutinous rice starch glycolate showed the best disintegrating properties. The results of modification of various starches may be different. This could be attributed that the different starches have the different compositions, such as amylose to amylopectin ratio and other components.

Table 3 Disintegration Times of Dicalcium Phosphate Tablets Containing Various Disintegrants.

Disintegrant	Mean DT of native form (sec)	Mean DT of modified form (sec)
Blank	> 3600	> 3600
Tapioca Starch	23.17 (2.22)	20.00 (2.82)
Rice starch	60.67 (1.21)	33.00 (2.82)
Corn starch	23.50 (2.42)	22.83 (1.72)
Glutinous rice starch	48.52 (3.20)	20.00 (1.41)
Wheat starch	314.33 (137.51)	21.50 (2.17)
Arrow root starch	28.33 (1.63)	27.00 (1.78)
Avicel^{R} pH 101	-	384.00 (21.40)
Explotab^{R}	-	24.17 (2.78)
Ac-Di-Sol^{R}	-	8.50 (0.83)
Polyplasdone^{R} XL	-	4.67 (1.03)

Hardness of 4-6 Kp.

Standard deviations are in parentheses.

A comparison study of the effect of various modified carboxymethyl starch on disintegration times of dicalcuim phosphate tablets with various effective disintegrants : Avicel^{R} pH 101, Explotab^{R}, Ac-Di-Sol^{R} and Polyplasdone^{R} XL at the same concentration (5%) showed that modified carboxymethyl starch showed better disintegrating properties than Avicel^{R} pH101 and Explotab^{R}, but worse than Ac-Di-Sol^{R} and Polyplasone^{R}XL. This could be explained that either the degree of carboxymethyl substitution were not optimum

or the carboxymethyl starch derivatives were soluble in water and formed viscous barrier which retarded the disintegration. A further modification to improve the property should be done to achieve the optimum disintegrating properties.

For lactose tablets as a model of soluble tablet system, the blank tablets showed poor disintegration. When the various types of native starches and modified carboxymethyl starches were used as tablet disintegrants, the disintegration times were decreased due to capillary action and swelling properties of starch grains in tablet causing the tablets disintegrated.

Compared to the disintegration times of dicalcium phosphate tablets, the disintegration times of lactose tablet containing native starches and carboxymethyl starches as tablet disintgrant at the same concentration were similar. This could be attributed that the disintegration process may be less important for the soluble tablet system because they can dissolve readily which are different from the poorly soluble tablets, the disintegration is the most important process to disintegrate the tablet into primary particles.

A comparison study of the effect of various modified carboxymethyl starches on disintegration times of lactose tablets with various effective disintegrants : Avicel^{R}pH101, Explotab^{R}, Ac-Di-Sol^{R} and Polyplasdone^{R}XL showed that Polyplasdone^{R} XL showed the best disintegrating property as shown in table 4.

Table 4 Disintegration Times of Lactose Tablets Containing Various Disintegrants.

Disintegrants	Mean DT of native form (sec)	Mean DT of modified form (sec)
Blank	615.33 (153.68)	615.33 (153.68)
Tapioca Starch	40.50 (2.58)	36.00 (2.36)
Rice starch	49.00 (2.82)	42.83 (3.43)
Corn starch	49.50 (1.87)	45.50 (4.23)
Glutinous rice starch	38.17 (2.36)	36.66 (2.16)
Wheat starch	36.00 (3.28)	34.66 (1.96)
Arrow root starch	51.67 (4.30)	44.33 (3.77)
Avicel^{R} pH 101		120.17 (4.33)
Explotab^{R}		41.33 (2.33)
Ac-Di-Sol^{R}		52.67 (5.00)
Polyplasdone^{R} XL		18.33 (1.36)

Hardness of 2-4 kp.

Standard deviations are in parentheses.

Disintegration time and dissolution time studies of erythromycin stearate tablets.

Among the native starches acting as tablet disintegrant of erythromycin stearate tablets, corn starch was the best disintegrant and in accordance with the dissolution study as shown in Table 5 and Figure 10.

Among the modified carboxymethyl starches as tablet disintegrants of erythromycin stearate tablets, carboxymethyl tapioca starch showed the best disintegrating property as shown in Table 5.

The dissolution profile of tablets containing carboxymethyl tapioca glycolate showed the highest dissolution profile as shown in Figure 11 and 12. Although the Polyplasdone^{R} XL showed the shortest disintegration time the dissolution profiles of the tablets containing Polyplasdone^{R} XL was lower than the one containing tapioca starch as tablet disintegrant. It was observed that the tablet containing Polyplasdone^{R} XL disintegrated not only into a tiny particle but also into large granules which were small enough to pass through the sieve of the disintegration tester. The large granules, rate of dissolution might need some time to disintegrate into smaller particle and then into primary particles before the dissolution occurred. Therefore, the dissolution rate decreased.

Table 5 Disintegration Times of Erythromycin Stearate Tablets Containing Various Disintegrants.

Disintegrants	Mean DT of native form (sec)	Mean DT of modified form (sec)
Blank	> 1800	> 1800
Tapioca Starch	209.83 (12.52)	76.66 (3.72)
Rice starch	341.00 (12.31)	154.83 (3.86)
Corn starch	144.83 (5.77)	103.66 (3.01)
Glutinous rice starch	174.66 (6.00)	98.83 (2.31)
Wheat starch	320.66 (2.42)	102.83 (5.11)
Arrow root starch	372.00 (2.42)	153.14 (5.72)
Avicel^{R} pH 101		> 1800
Explotab^{R}		131.33 (7.20)
Ac-Di-Sol^{R}		92.83 (5.70)
Polyplasdone^{R} XL		61.50 (4.37)

Hardness of 4-6 kp.

Standard deviations are in parentheses.

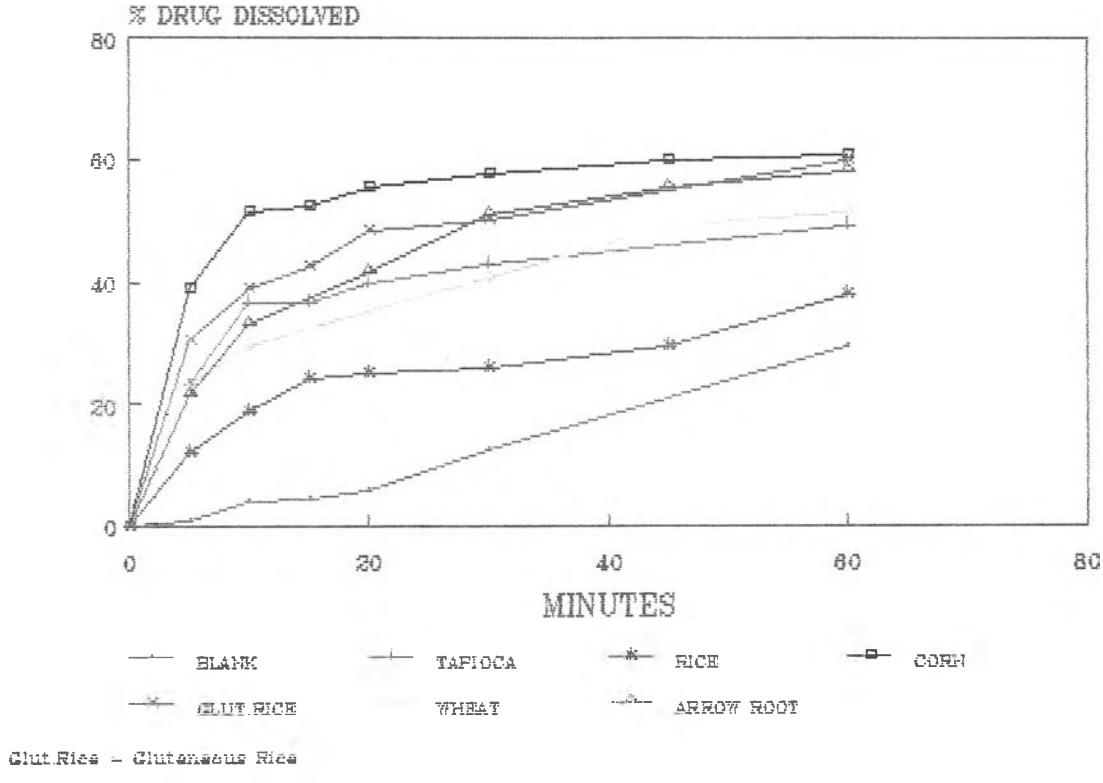

Figure 10 Dissolution Profiles of Erythromycin Stearate Tablets Containing 4 % Various Native Starches as Disintegrant.

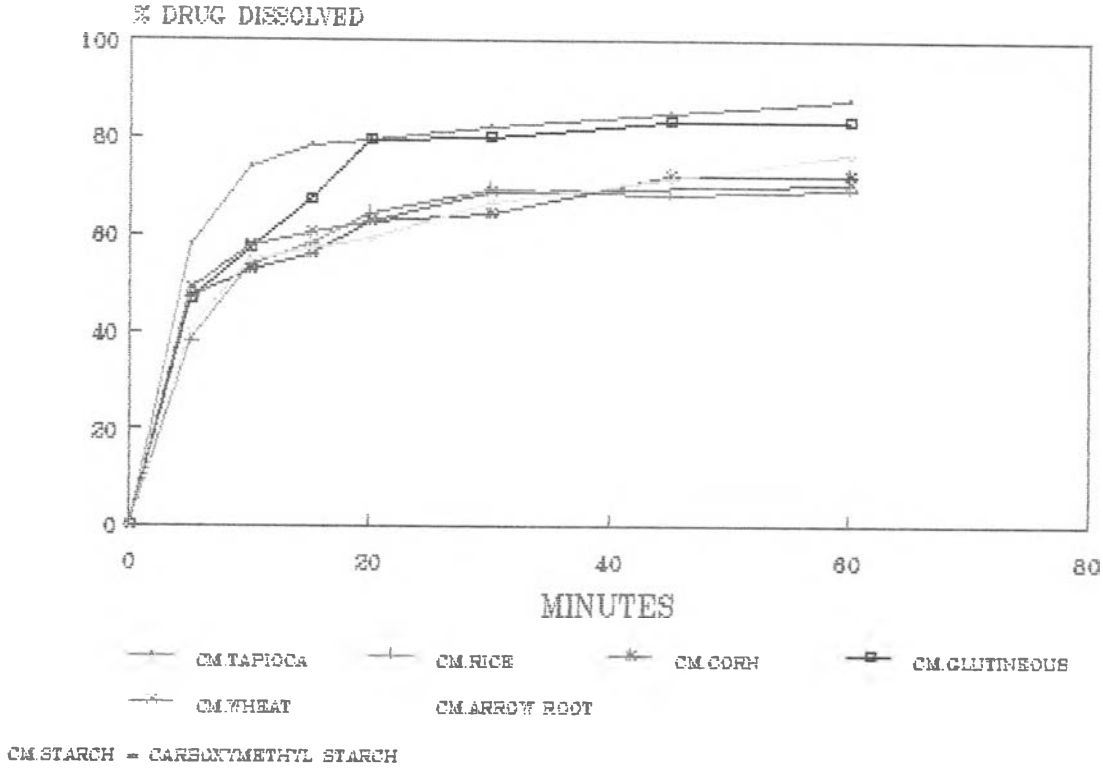

Figure 11 Dissolution Profiles of Erythromycin Stearate Tablets Containing 4 % Various Carboxymethyl Starches as Disintegrant.

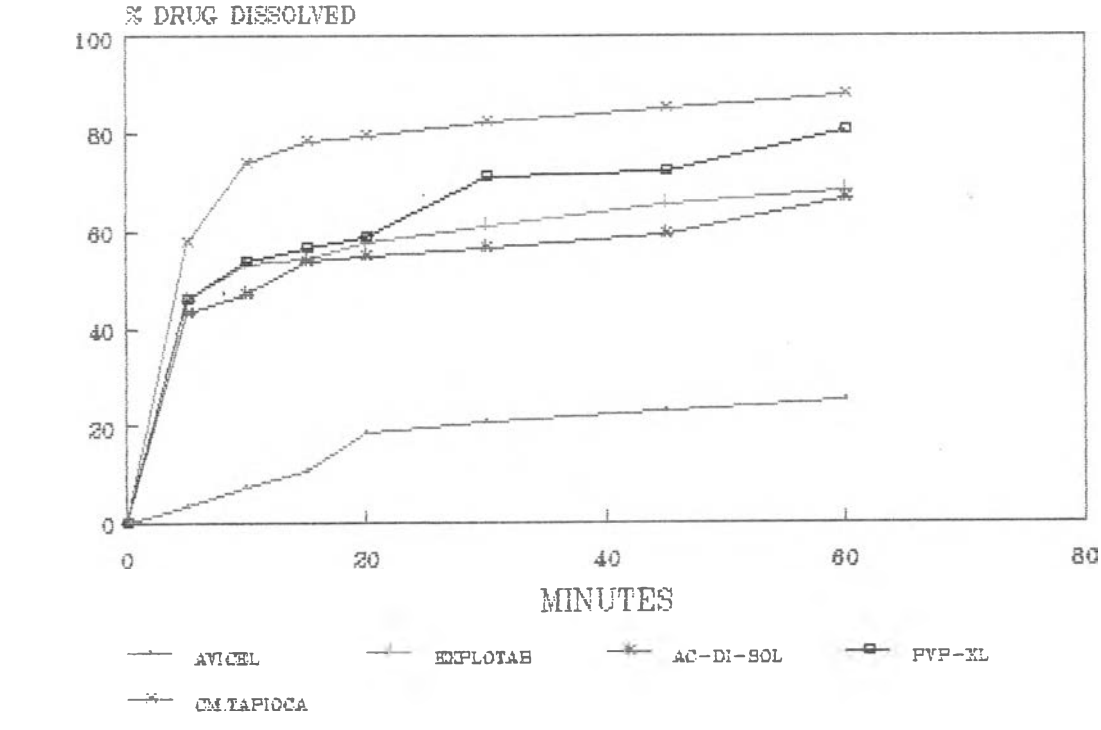

Figure 12 Dissolution Profiles of Erythromycin Stearate Tablets Containing 4 % Various Disintegrants.

Figure 13 illustrated the dissolution profiles of erythromycin stearate tablets containing plain tapioca starch, modified carboxymethyl tapioca starch as tablet disintegrant. The dissolution profile of tablet containing modified carboxymethyl tapioca starch showed better dissolution profile than the one cantaining plain tapioca starch and the blank tablets.

Conclusions

The tablets containing native starches as tablet disintegrants showed more rapid disintegration than the blank tablet in all case. This can be explained that due to the capillary action of starch grains and they swell when contact with water causing the tablet disintegrate.

The modified carboxymethyl starches can markedly decrease the disintegration times of dicalcuim phosphate tablets and erythromycin stearate tablets. They can also noticeably increase dissolution profile of erythromycin stearate tablets. This could be explained that the modified starches were hydrophilic but were not completely water soluble. When they were exposed to water, the modified starch grains swelled and caused tablet disintegrate into primary particles with increasing surface area of the drug then facilitating the tablet to dissolve.

Although all of the native starches which have been studied can be modified by carboxymethyl substitution to act as highly effective disintegrants the tapioca starch appeared to be the best as it gave the best results for disintegration and dissolution studies. Tapioca is commonly cultivated in Thailand. As far as the literature search was concerned there is no report on the chemical modification of tapioca starch as a tablet super disintegrant.

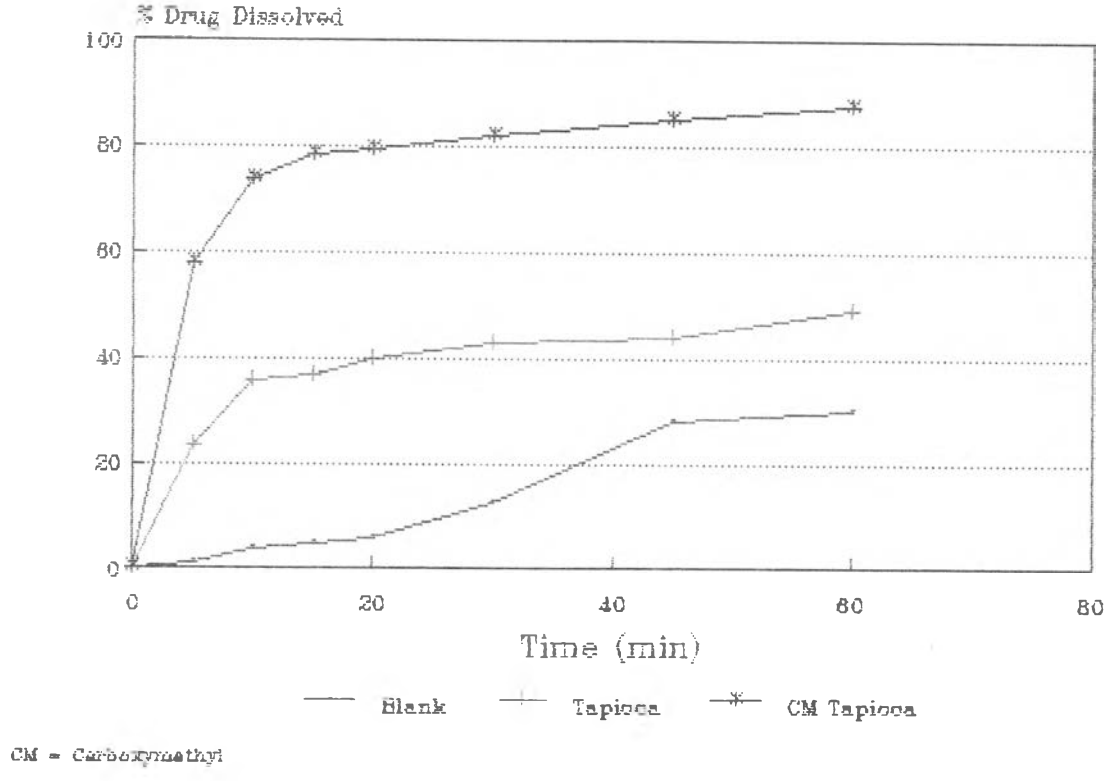

Figure 13 Comparative Dissolution Profiles of Erythromycin Stearate Tablets Containing 4 % Native Tapioca Starch and 4 % Carboxymethyl Tapioca Starch as Disintegrant.