# CHAPTER 3

# RESULTS AND DISCUSSION

## 3.1 Determination of amylose content

The amylose content of native rice starch (RS) was determined using the iodine spectrophotometric method according to Juliano (Juliano, 1971). Figure 3.1 shows a standard curve verified based on five concentrations of pure amylose. This curve was utilized for determination the amylose content of RS. The solution sample form RS gave the absorbance at 620 nm as 0.249. Then, the amylose content of RS was calculated and provided the value as 25.50%. The value is in agreement with previous report for native rice starch by Kittipongpatana et al. (2007) and Singh (2003) as shown in Table 1.2.

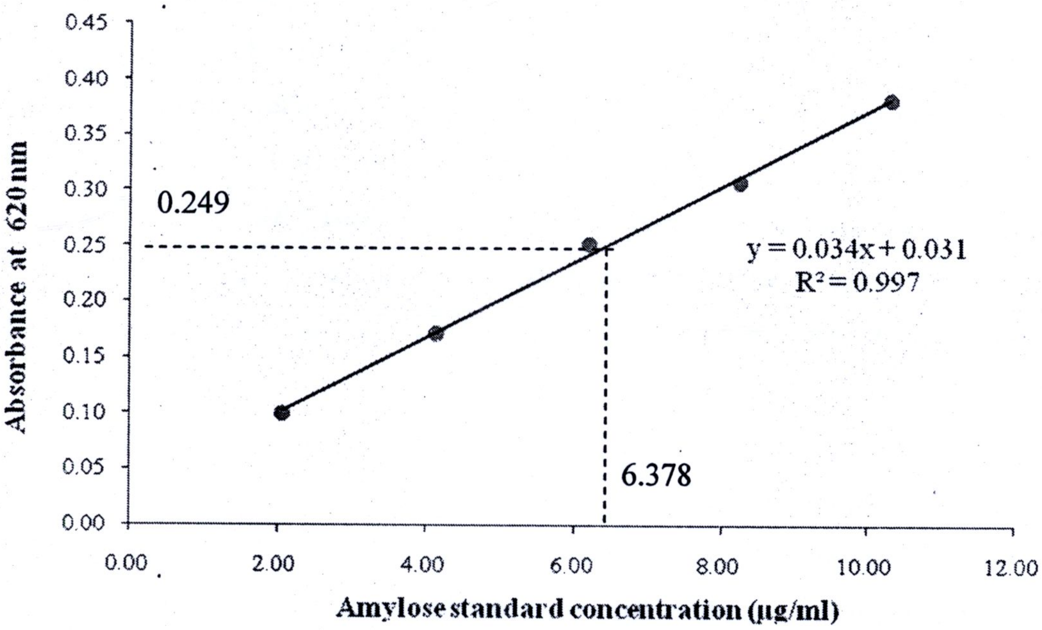


**Figure 3.1** Amylose standard curve

## 3.2 Determination of degree of substitution (DS), solubility, swellability and degree of cross-linking (DC)

Cross-linked carboxymethyl rice starches (MRSs) were prepared to yield twelve different MRSs; six MRS-M (MRS modified in methanol medium) and six MRS-I (MRS modified in 2-propanol) (shown in Table 3.1). The appearance of each MRS and RS is white powder and it is shown in Figure 3.3 and 3.4, respectively. DS value of MRS-M and MRS-I were between 0.30-0.38 and 0.41-0.50, respectively. The results showed that higher DS value was obtained when 2-propanol medium was used. An organic solvent used in reaction was selected to provide good solubility for carboxymethylating agent and good selectivity for carboxymethylation without formation of byproduct. Similar results were reported for carboxymethyl kudzu root starch (Wang et al., 2010) and carboxymethyl mungbeen starches (Kittipongpatana et al., 2006). These researchers presented that modification in methanol medium yielded lower DS products of carboxymethylation than 2-propanol medium. In addition, Tigen et al. (2001) reported that the optimal efficiency was presented for carboxymethylation of potato starch in 2-propanol–water medium.

Table 3.1 also shows the solubility of MRSs. Normally, native starch was not soluble in cold water unless it was functional modified such as modification by carboxymethylation. In this research, the soluble modified rice starches were MRS-M-01, MRS-M-02, MRS-I-01, and MRS-I-02. These MRSs provided DS value as 0.30, 0.35, 0.41, and 0.42, respectively. DS value of the others, were not soluble but swellable in water, was in range of 0.30-0.50. The result indicated that solubility of MRSs was not depended on DS.

Figure 3.5 presents the comparison of swellability of RS, MRSs and two commercial superdisintegrants (SSG and CCS). The swelling volume of RS was the lowest compared with that of the others as below 1.0 ml. The results revealed that swelling volume of MRSs decreased when the cross-linking level increased. This is due to the increasing of cross-linking density causing stimulates rigid networks forming (Silva et al., 2006). The highest swelling (11.43 ml) was obtained from MRS-M-03. Interestingly, this value was 19, 4 and 2 times higher than that of RS and two commercial superdisintegrants; CCS and SSG, respectively. The results showed that MRSs could be applied as a pharmaceutical excipient possible as tablet disintegrant.

In literatures, the swellability of modified cross-linked starch had been reported. Van Hung and Morita (2005) presented that cross-linking of the hydroxypropylated starches obstructed granule swelling and reduced paste viscosity and clarity. In addition, cross-linking of starch with phosphorus oxychloride ($POCl_3$) was investigated by Mirmoghtadaie et al. (2009). They found the similar results for swelling power of cross-linked starch compared with ours. The swelling factor of oat starch decreased when the amount of cross-linking agent increased. They gave the reason that cross-linking reinforces bonding between starch chains. Therefore, an increase in opposition of the granules to swelling with increasing degree of cross-linking was observed. Furthermore, cross-linking strengthen the structure of starch granules and restricts water absorption by limit the mobility of starch chains in the amorphous region (Gunaratne and Corke, 2007).

The Figure 3.6 show the relationship between cross-linking level and swelling volume of MRS-M and MRS-I. MRS-M and MRS-I revealed the resemble trend of the relationship. This observation confirmed that the level of cross-linking had effect to swelling volume of MRS. The swelling volume of MRS gradually declined when the level of cross-linking was higher. However, the swellability of the MRS seemed to be stable at too high cross-linking level of the reaction (>10). The similar result was reported previously by Wattanachant et al. (2003). They presented the linear regression of swelling power of dual-modified sago starches hydroxypropylated with different levels of propylene oxide (cross-linking agent).

In this study, degree of cross-linking (DC) was a number that indicated the cross-linking level in cross-linked modified starches and it was between 0 and 1. The DC was directly depending on swellability of MRS. The DC of MRSs is presented in table 3.1. The result showed DC of the MRSs was in range of 0.0-0.89. Because of the very low level of cross-linking reaction with epichlorohydrin for MRS-M-02 and MRS-I-02, the DC value of them was suppose to be nearly zero. The level of cross-linking increased the DC and decreased the swellability of cross-linked starch.

**Table 3.1** Degree of substitution (DS), water solubility and DC of MRSs modified with different cross-linking levels

| **Samples** | **Cross-linking level** | **DS** | **DC** | **Solubility in water** |
|---|---|---|---|---|
| MRS-M-01 | 0.0 | 0.2981 | 0 | ✓ |
| MRS-M-02 | 0.5 | 0.3486 | Nearly 0 | ✓ |
| MRS-M-03 | 1.0 | 0.2937 | 0.43 | × |
| MRS-M-04 | 3.0 | 0.3701 | 0.65 | × |
| MRS-M-05 | 10.0 | 0.3443 | 0.85 | × |
| MRS-M-06 | 15.0 | 0.3027 | 0.89 | × |
| MRS-I-01 | 0.0 | 0.4138 | 0 | ✓ |
| MRS-I-02 | 0.1 | 0.4236 | Nearly 0 | ✓ |
| MRS-I-03 | 1.0 | 0.4276 | 0.59 | × |
| MRS-I-04 | 3.0 | 0.4961 | 0.78 | × |
| MRS-I-05 | 7.5 | 0.4262 | 0.86 | × |
| MRS-I-06 | 15.0 | 0.4173 | 0.88 | × |

MRS-M-01

MRS-M-02

MRS-M-03

MRS-M-04

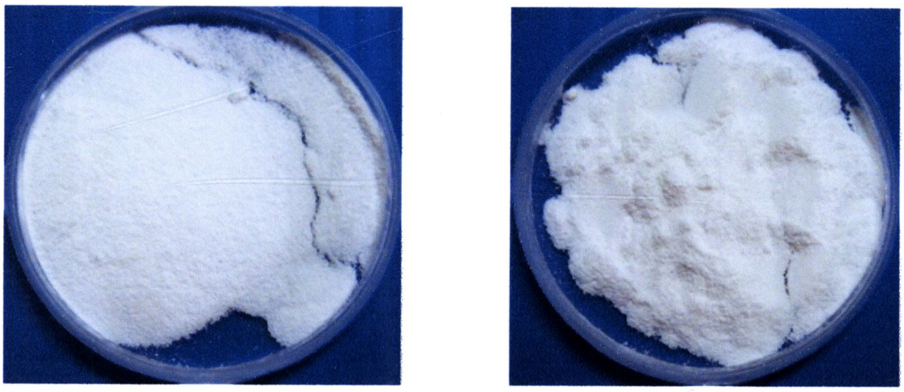
MRS-M-05

MRS-M-06

**Figure 3.2** Characteristic of MRS-Ms

MRS-I-01 MRS-I-02

MRS-I-03 MRS-I-04



MRS-I-05 MRS-I-06

**Figure 3.3** Characteristic of MRS-Is

RS

**Figure 3.4** Characteristic of native rice starch (RS)

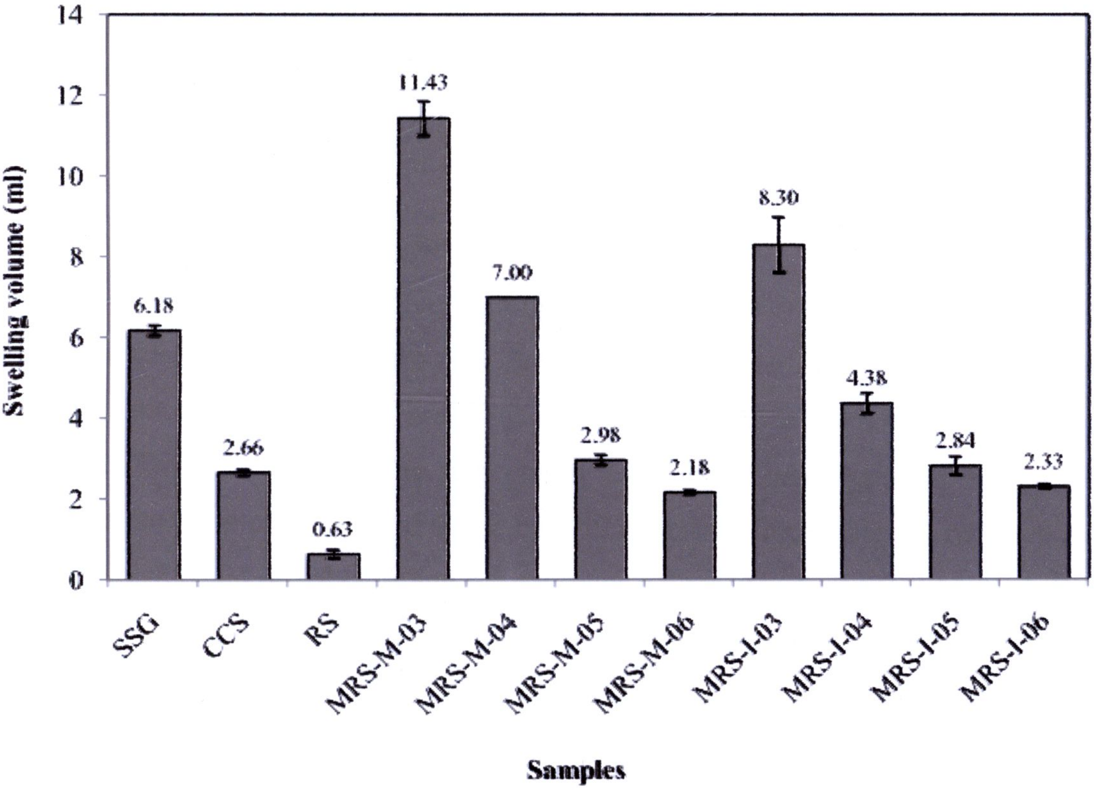


**Figure 3.5** Swelling volume of commercial superdisintegrants; SSG and CCS, native rice starch (RS) and modified rice starches (MRSs)

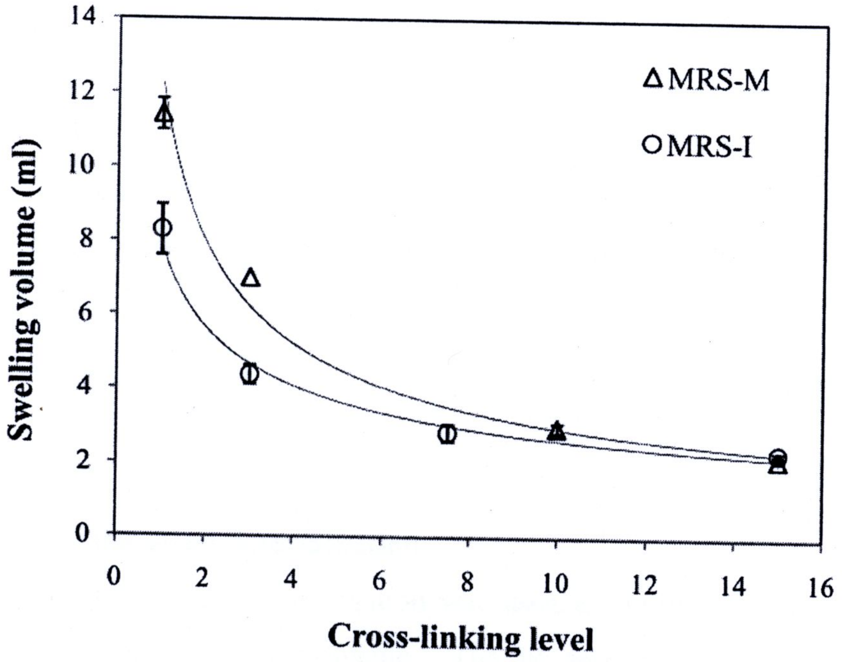


**Figure 3.6** The relationship between cross-linking level and swelling volume of MRS-M (MRS modified using methanol as a medium) and MRS-I (MRS modified using 2-propanol as a medium)

### 3.3 pH of solution and clarity of paste

The pH of water soluble modified starch (1% w/v) range between 6.8 and 7.6. The clarity of starch paste (1% w/v) was investigated based on percent light transmission (%T) at λ=650 nm. The absorbance (A) at λ=650 nm could be calculated from %T value. The respectively lower and higher value of %T and A indicated the more cloudiness of the sample. The results from table 3.2 revealed the MRSs, which could be solvable and form viscous gel mass such as MRS-M-01, MRS-M-02, MRS-I-01, and MRS-I-02, obviously gave the higher %T value compared to that of native rice starch. This observation was related with the paste clarity of carboxymethyl starch from corn, tapioca, rice and glutinous rice starch in literatures (Kittipongpatana et al., 2006; Tehkhunmag, 2007). They also found that the carboxymethyl starch showed more clarity of paste compared with that of native starch.

**Table 3.2** The pH and clarity of paste of native and modified starch

| Samples | pH | T (%) | A |
|---|---|---|---|
| RS | 7.4 | 4.134 | 1.384 |
| MRS-M-01 | 7.0 | 38.386 | 0.416 |
| MRS-M-02 | 6.8 | 8.202 | 1.086 |
| MRS-I-01 | 7.5 | 44.556 | 0.351 |
| MRS-I-02 | 7.3 | 21.837 | 0.661 |

### 3.4 Infrared spectroscopy determination

The IR spectroscopy investigation was used to confirm the substitution of carboxymethyl group in starch molucule. The IR spectra of RS and MRSs are presented in Figure 3.7 to 3.19. RS and all MRSs had the same functional groups. The broad absorption band at 3350 cm$^{-1}$ is due to the stretching frequency of the –OH group. The –CH peak show the band at 2929 cm$^{-1}$. The bands at 1420 and 1320 cm$^{-1}$ is assigned to –CH$_2$ scissoring and –OH bending vibration, respectively. The band at 1060 cm$^{-1}$ is due to –CH–O–CH$_2$ stretching (Kondo, 1997; Yanli et al., 2009). The presence of a strong band at 1606.84 cm$^{-1}$ of COO– groups in the IR spectrum of MRSs indicated presence of carboxymethyl group. Intensity of the peak of COO– group in IR spectrum related with the DS value of MRS, DS increased when the intensity of the peak increased. Similar observations have been reported previously for carboxymethyl mungbeen starches (Kittipongpatana et al., 2006), carboxymethyl chinese yam starches (Yanli et al., 2009), carboxymethyl rice starches (Kittipongpatana et al., 2007), and carboxymethyl water yam starches (Lawal et al., 2008a).

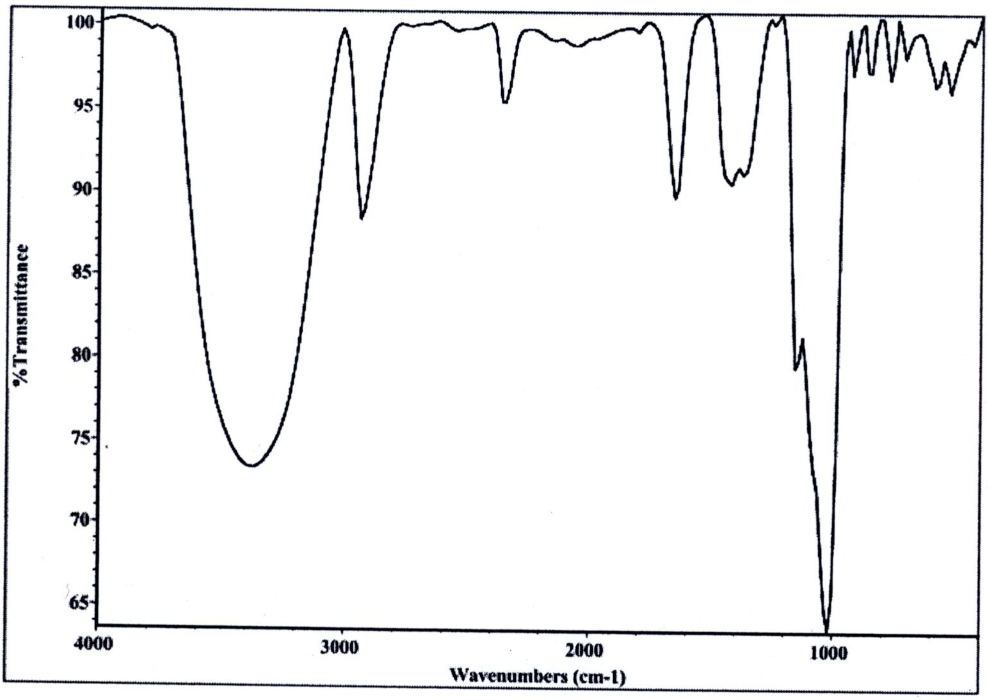


**Figure 3.7** IR Spectrum of native rice starch

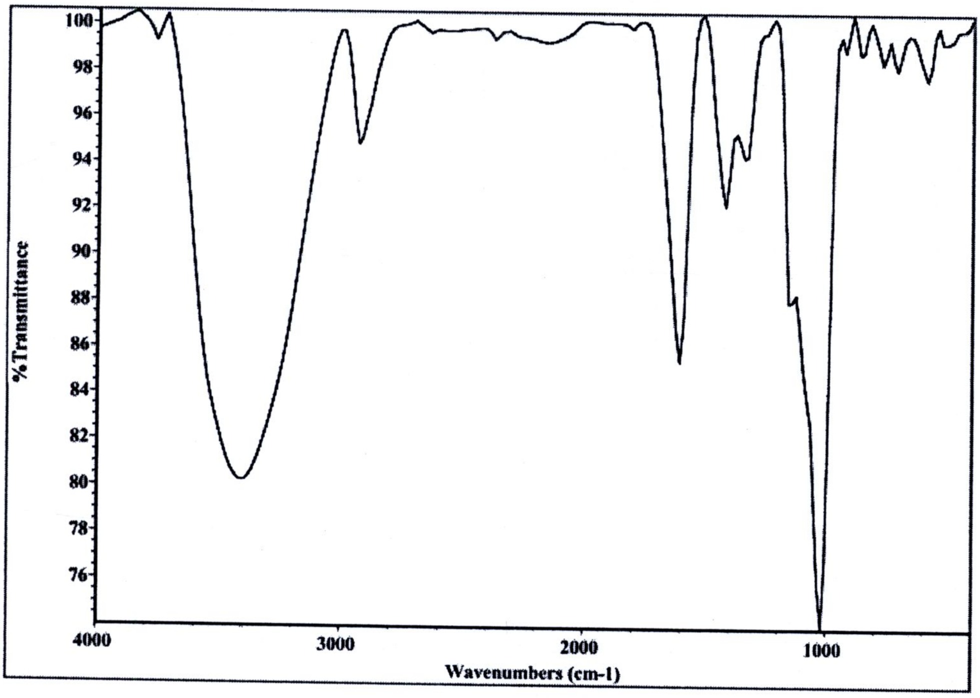


**Figure 3.8** IR Spectrum of MRS-M-01

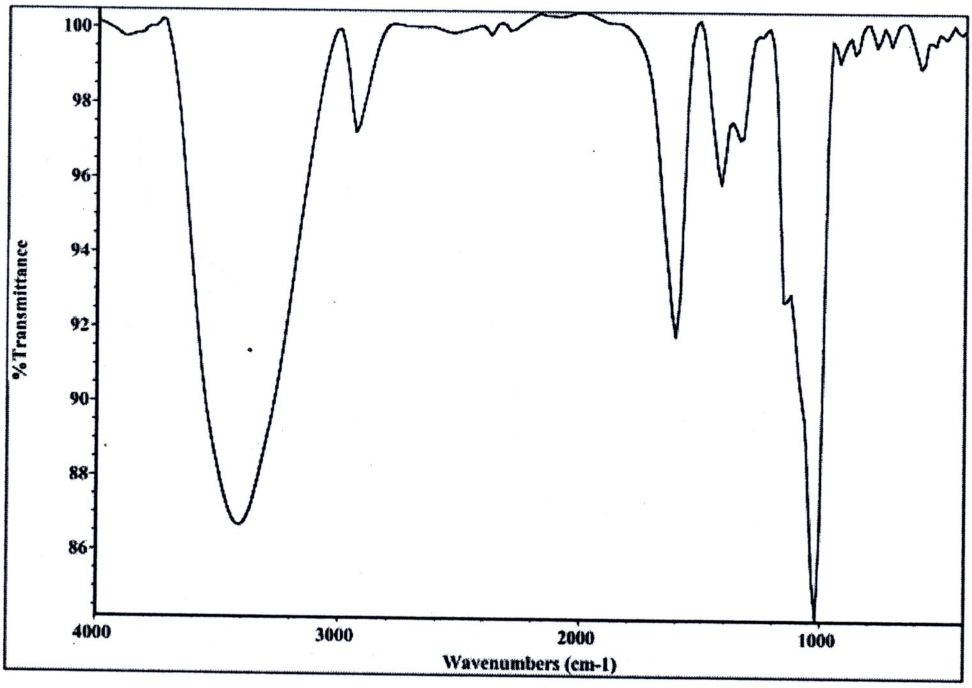


**Figure 3.9** IR Spectrum of MRS-M-02

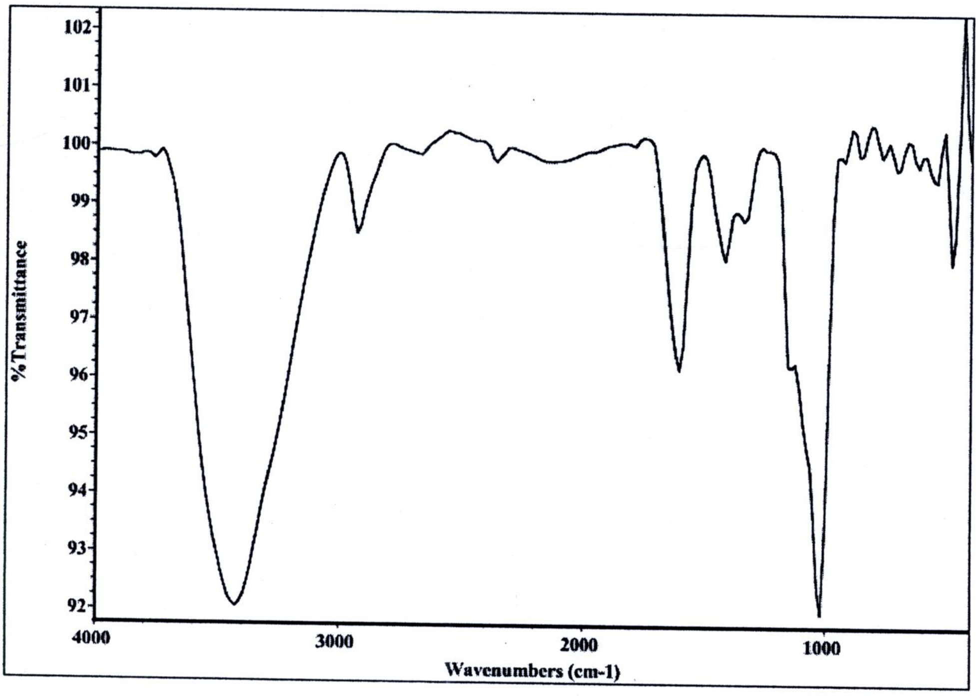


**Figure 3.10** IR Spectrum of MRS-M-03

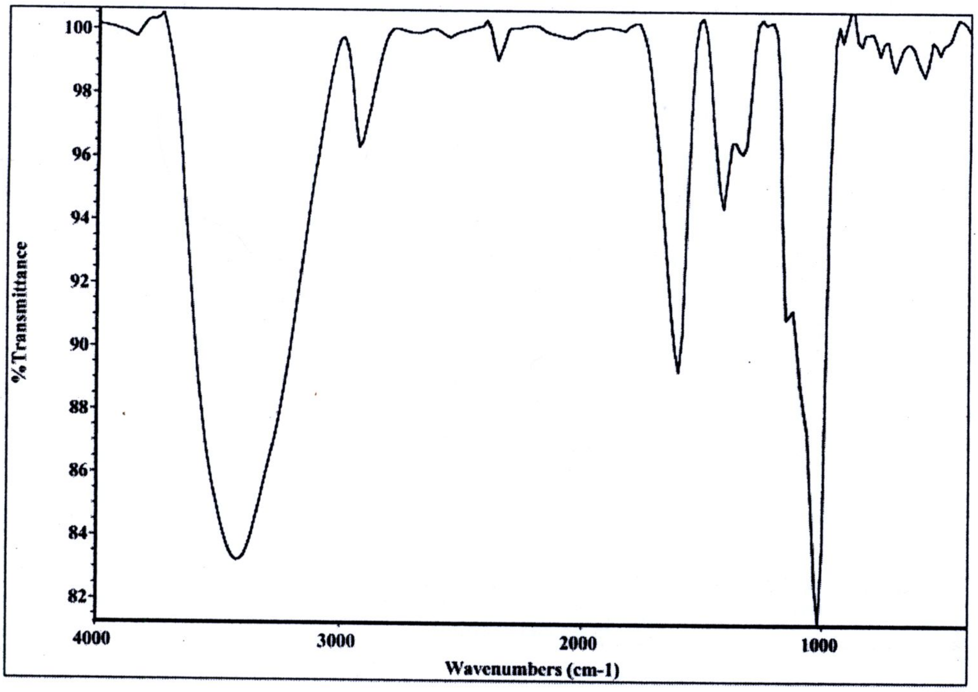


**Figure 3.11** IR Spectrum of MRS-M-04

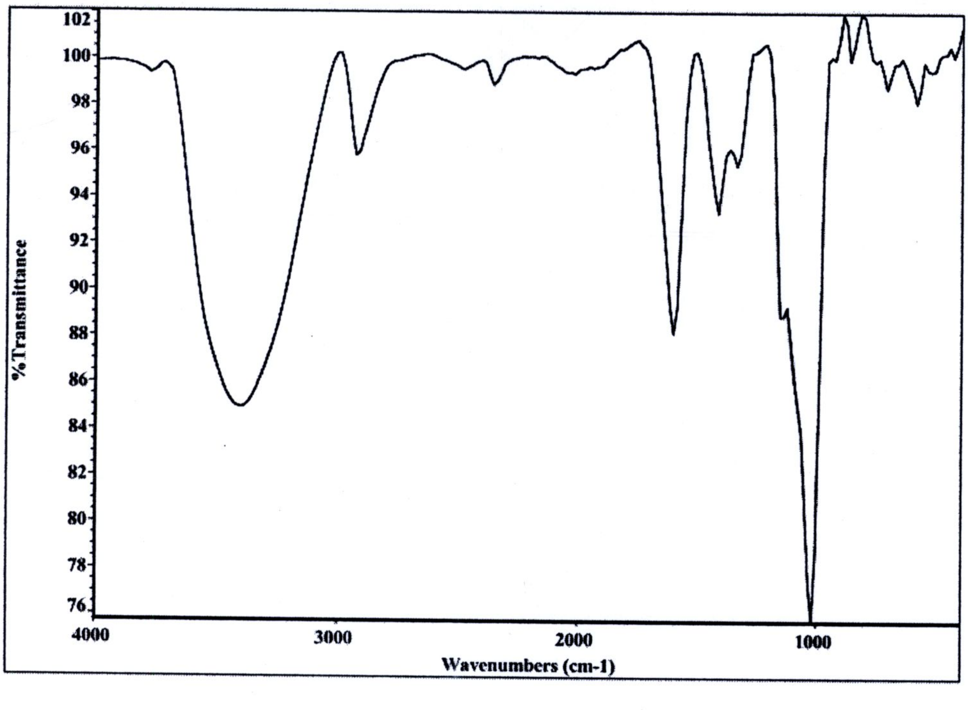


**Figure 3.12** IR Spectrum of MRS-M-05

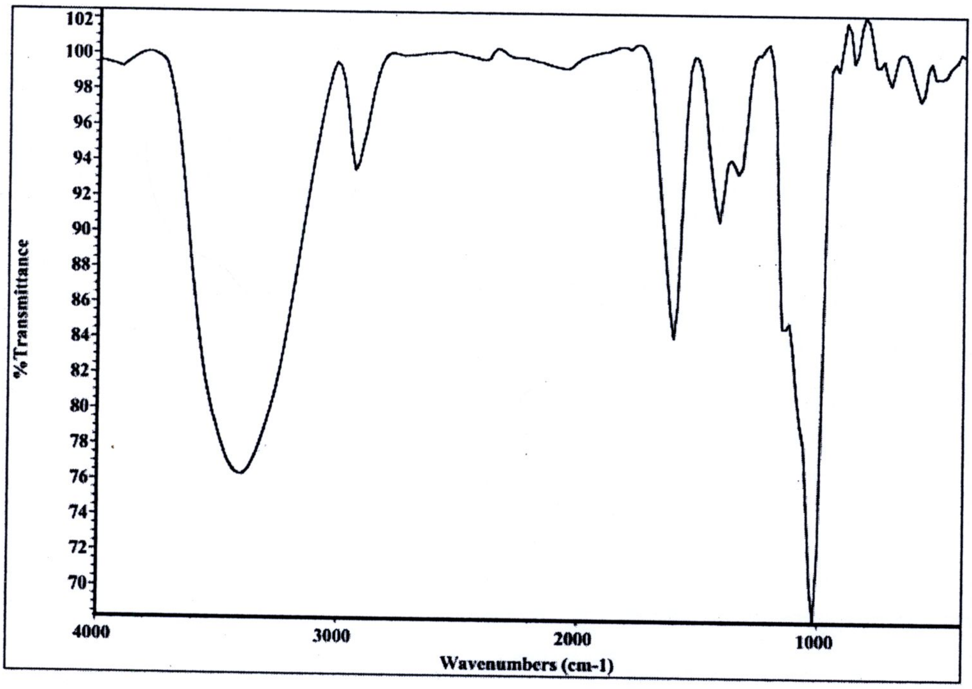


**Figure 3.13** IR Spectrum of MRS-M-06

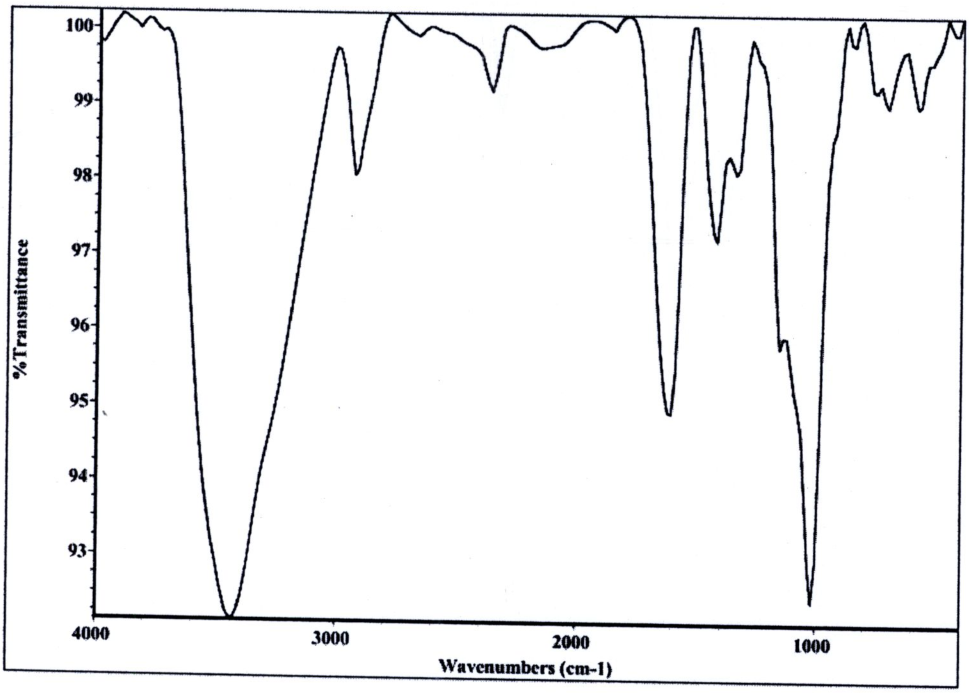


**Figure 3.14** IR Spectrum of MRS-I-01

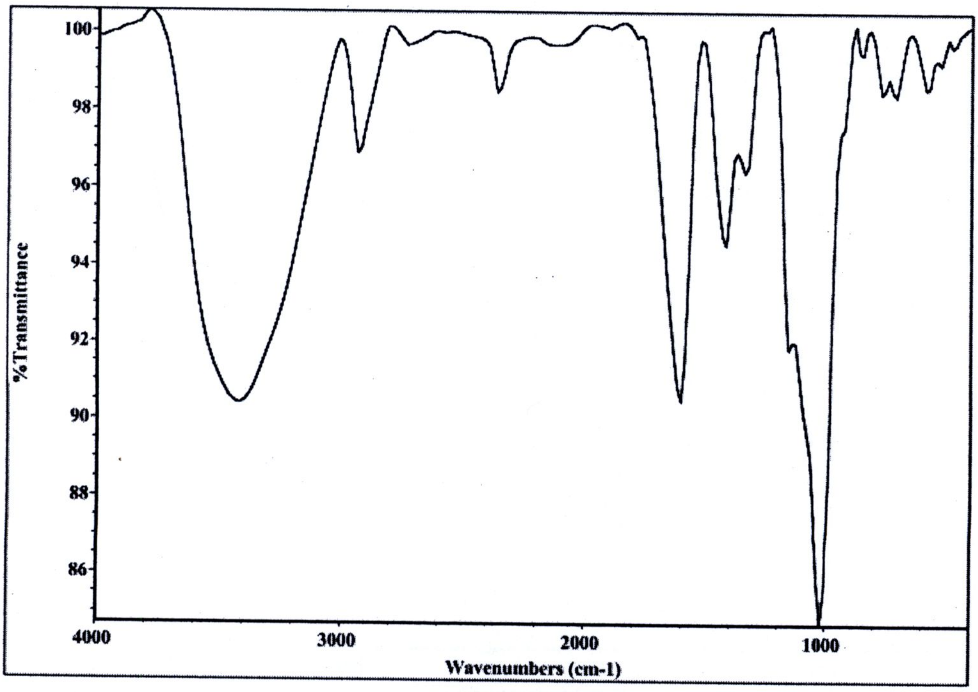


Figure 3.15 IR Spectrum of MRS-I-02

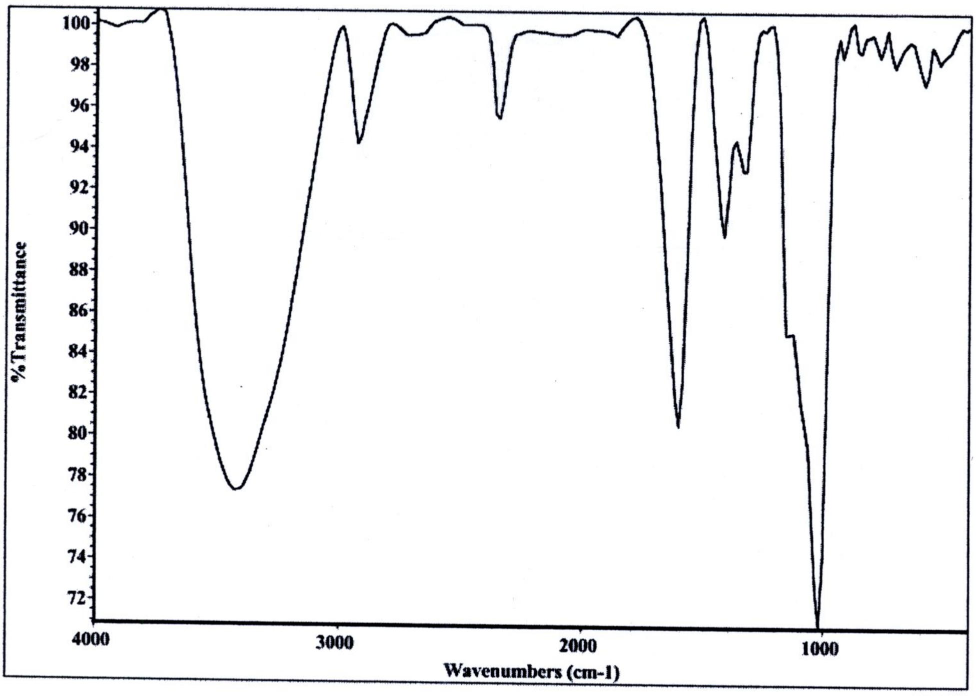


Figure 3.16 IR Spectrum of MRS-I-03

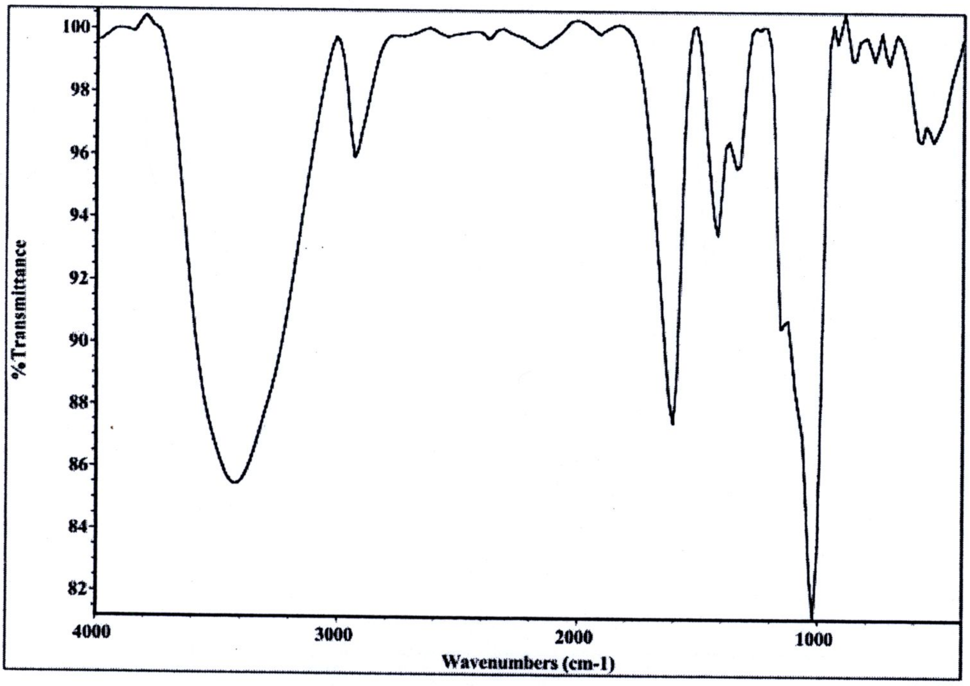


**Figure 3.17** IR Spectrum of MRS-I-04

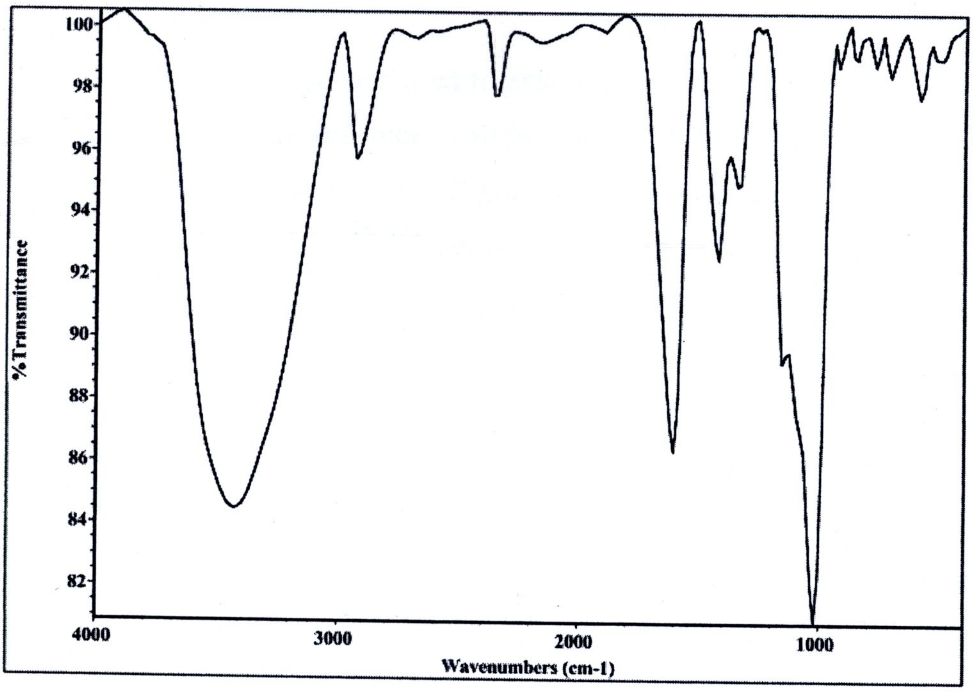


**Figure 3.1**8 IR Spectrum of MRS-I-05

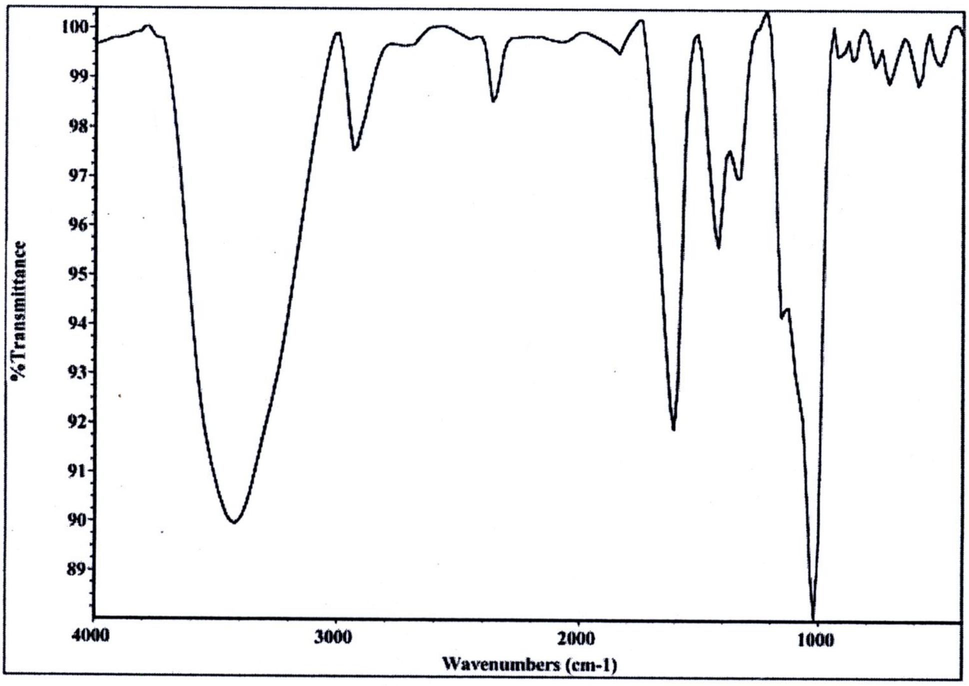


**Figure 3.19** IR Spectrum of MRS-I-06

### 3.5 X-ray diffraction

The X-ray diffraction was used to examine the crystal behavior of the MRS compared with that of RS and other MRSs. X-ray diffractograms of native and modified rice starches are presented in Figure 3.20. The X-ray diffraction pattern of RS indicated strong reflections of diffraction angle 2θ at 15.1, 17.9 and 23.0. This is in agreement with those reported by Kittipongpatana et al. (2007), Tehkhunmag (2007), and Majzoobi et al. (2009) that rice starches exhibit an A-type crystal pattern like other cereal starches. Each MRS showed the similar X-ray diffraction pattern with RS and a slight decrease in the intensity of reflection signal was occurred. This result showed that the modification of carboxymethyl substitution did not alter the crystallinity of the starches. In addition, the result indicated that crystallinity change was not influenced by ECH concentration in these MRSs. Majzoobi et al. (2009) reported that cross-linking did not alter the crystalline pattern of starch. The slight change in X-ray diffractograms of all MRS-M compared with that of RS due to effect of methanolic solvent utilized as medium in reaction. The similar phenomenon had been presented previously in carboxymethyl starches from tapioca starch (Tehkhunmag et al., 2008), rice starch, corn starch (Tehkhunmag, 2007) and mungbean starch (Anutrakulchai, 2010; Kittipongpatana et al., 2006). In contrast, Wang et al. (2010) reported that remarkable changes in crystallinity of modified starches were observed due to the effect of the alkaline environment.

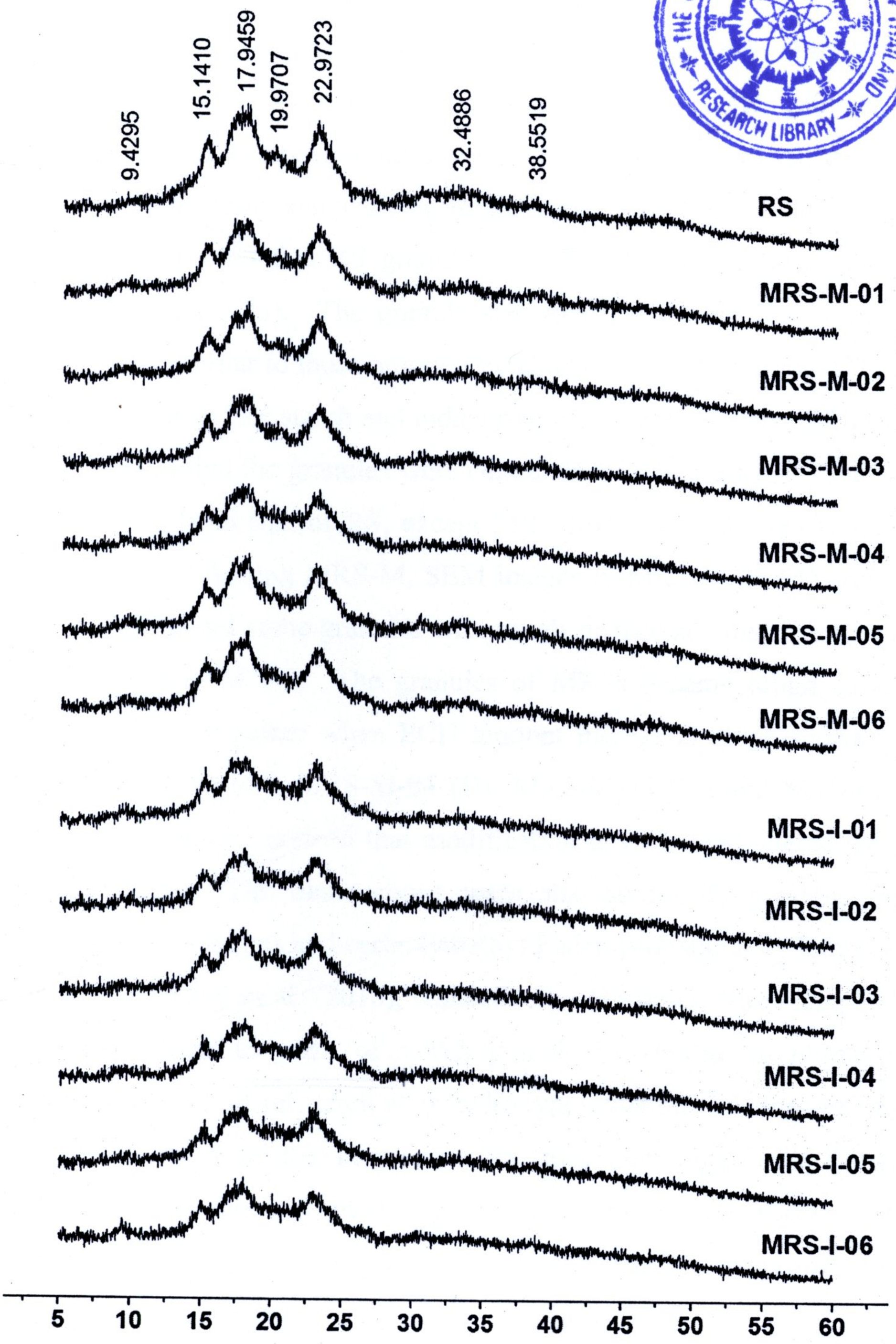


**Figure 3.20** Representative X-ray diffraction patterns of native and modified rice starches

## 3.6 Scanning electron microscopy

The morphology of RS and all MRSs was investigated to observe the effect of carboxymethylation and cross-linking on the surface of starch granules. Figure 3.21 and 3.22 showed scanning electron micrographs (SEM) of MRSs modified with diferent types of medium and various amounts of ECH. Investigation of granule surface by SEM showed that RS granules were polygonal with little unsystematic shaped ruins (Figure 3.23). The granule size range was from 2 to 7 µm. These observations were similar to those reported by Kittipongpatana et al. (2007) and Singh et al. (2006) for native rice starch and indica rice starch, respectively. SEM images of all MRS-I revealed that the granules were conglomerated into a hunk. They were not appeared different from that of RS, except MRS-I-03 which showed some granules with rough surface. Among MRS-M, SEM images of MRS-M-01 (A) and MRS-M-02 (B) granules showed some granules with rough surface and dispersion of granules compared with those of RS. The granules of MRSs became rough, grooved and gradually assembled together when ECH amount increased which showed in SEM images of MRS-M-03 (C), MRS-M-04 (D), MRS-M-05 (E), and MRS-M -06 (F), respectively. The results noticed that modification environment altered the granular structure of MRSs. The observations were also similar to previous report for carboxymethyl rice starches and carboxymethyl kudzu root starch by Kittipongpatana et al. (2007) and Wang et al. (2010), respectively. However, Van Hung and Morita (2005) presented that the size of starch granule influenced on physicochemical properties of modified wheat starch after hydroxypropylation and cross-linking. They revealed that surfaces of the large granules underwent significant damage after modification than did those of small granules. The cross-linking affected the surface of the granules only slightly for the large granule, whereas hydroxypropylation caused the whole surface of granules.

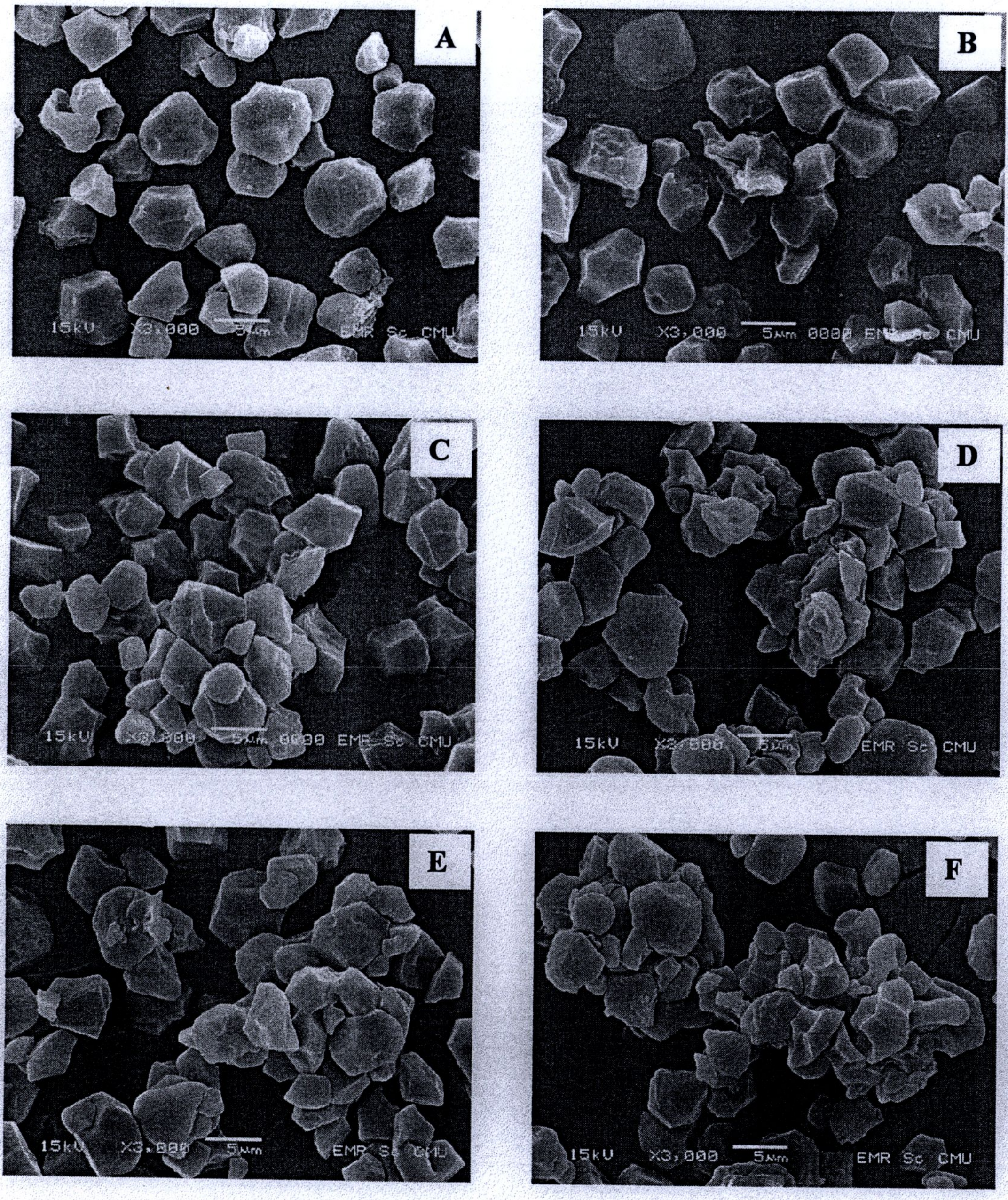


**Figure 3.21** Scanning electron micrographs of modified rice starches; (A) MRS-M-01; (B) MRS-M-02; (C) MRS-M-03; (D) MRS-M-04; (E) MRS-M-05; (F) MRS-M-06; magnification 3000X

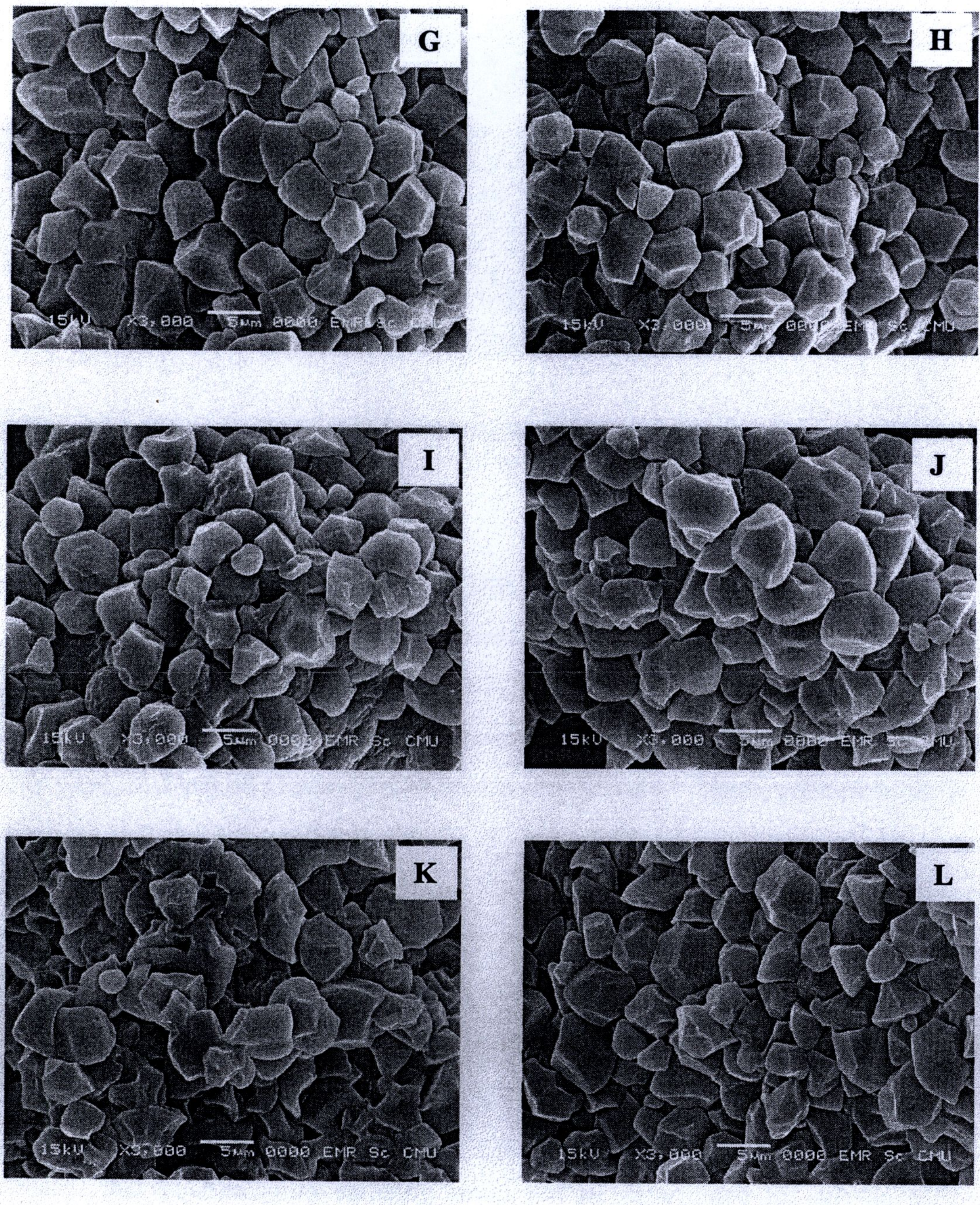


**Figure 3.22** Scanning electron micrographs of modified rice starches; (G) MRS-I-01; (H) MRS-I-02; (I) MRS-I-03; (J) MRS-I-04; (K) MRS-I-05; (L) MRS-I-06; magnification 3000X

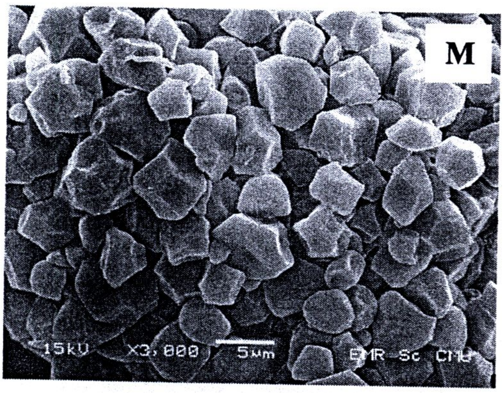


**Figure 3.23** Scanning electron micrographs of native rice starches (M); magnification 3000X

## 3.7 Differential scanning calorimetry (DSC)

The differential scanning calorimetry (DSC) thermograms of RS, MRS-M-03, and MRS-I-02 are presented in Figure 3.24. The onset temperature ($T_o$) of the RS was 70.65±0.22°C while the peak temperature ($T_P$) and the enthalpy of gelatinization ($\Delta H$) were 74.11±0.08°C and 6.60±0.04 J/g respectively. Starch gelatinization is a procedure that the intermolecular bonds of starch molecules are broke down in the presence of water and heat. Then, hydrogen bonding sites of starch can absorb more water. Intrusion of water increases randomness in the general structure and reduces amount and size of crystalline regions. The heated environment makes crystalline regions to be diffused thus the chains start to separate into an amorphous form (Whistler et al., 1984b). The DSC thermogram of all MRSs was in similar trend (data not shown) that the gelatinization peak was not observed. The result of the DSC indicated that gelatinization enthalpy could not be determined for all the MRSs, irrespective of the DS value. This phenomenon is demonstrative that amorphous region of starch granules increased after carboxymethylation (Lawal et al., 2008b). The related trend was also noticed in previous study for carboxymethyl starches from water yam (*Dioscorea alata*) starch (Lawal et al., 2008a) and pigeon pea starch (Lawal et al., 2008b).

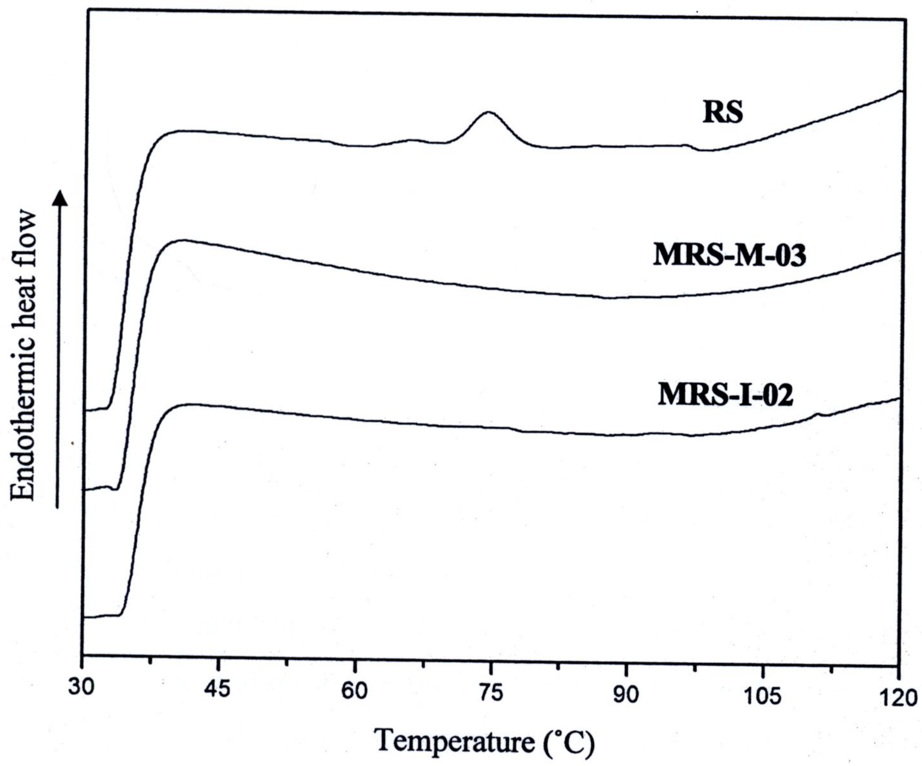


**Figure 3.24** DSC thermogram of native rice starch (RS) and its derivatives

### 3.8 Water uptake

The water uptake profile is an important investigation to determine the potential of materials as a tablet disintegrant (Kittipongpatana et al., 2010). The water uptake profiles of RS and each MRS, presented in Figure 3.25 and 3.26, showed that RS could absorb minimal water (below 1.0 ml). The maximum water uptake was observed in MRS-I-03 and it was 11.5, 2.6, and 1.6 times higher than that of RS, CCS, and SSG, respectively. The profiles of MRSs can be divided into two groups. The first group showed faster uptakes and slowing down saturation uptake within a few min. Interestingly, the water uptake behavior of this group was similar to those of two commercial superdisintegrants; SSG (Explotab®) and CCS (Ac-di-sol®). These profiles were characteristic of the MRSs modified with higher ECH amount such as MRS-M-05, MRS-M-06, MRS-I-03, MRS-I-04, MRS-I-05, and MRS-I-06. The other group presented uptake of water slowly and no saturation in 1 h. This phenomenon was observed from MRSs modified with lower amount of ECH. While, MRS-M-01, MRS-M-02, MRS-I-01, and MRS-I-02 could be soluble and gel forming was also occurred when they uptake the water thus they could uptake water slowly. The gel formed resisted water transmissibility to dry part of modified starch. This phenomenon was similar to the profile of modified mungbean starch (CMMS) by Anutrakulchai (2010). They found that CMMS (without cross-linking) could uptake the water slowly. Moreover, cross-linking caused reduction of solubility and swellability of MRSs. The faster uptake of water probably was caused of no gel forming while uptake of the water.

Figure 3.27 shows the relationship between cross-linking levels and water uptake of MRS-M and MRS-I. For result of MRS-M, the water uptake of MRS increased with increasing of cross-linking level (0-3% ECH) but it decreased with increasing of cross-linking level beyond 3% ECH. The highest water uptake value (7.5±0.4 ml) was obtained from MRS-M cross-linked with 3% ECH (MRS-M-04). In term of MRS-I, the trend of result was similar to MRS-M presented above. The water uptake of MRS increased when cross-linking level increased from 0 to 1% ECH. However, it diminished when cross-linking level increased after 1% ECH. MRS-I cross-linked with 1% ECH (MRS-I-03) gave the highest water uptake value as 10.0±0.4 ml. The results related with swellability investigation in previous experiment. The MRS which contained higher swelling value could uptake water much more than the others containing lower swelling value, except the MRS-M-03. The MRS-M-03 provided the water uptake value less than the MRS-M-04, although it got the swellability more than another one. This is due to some part of MRS-M-03 could form gel which is a water transmissibility resister when it uptake the water.

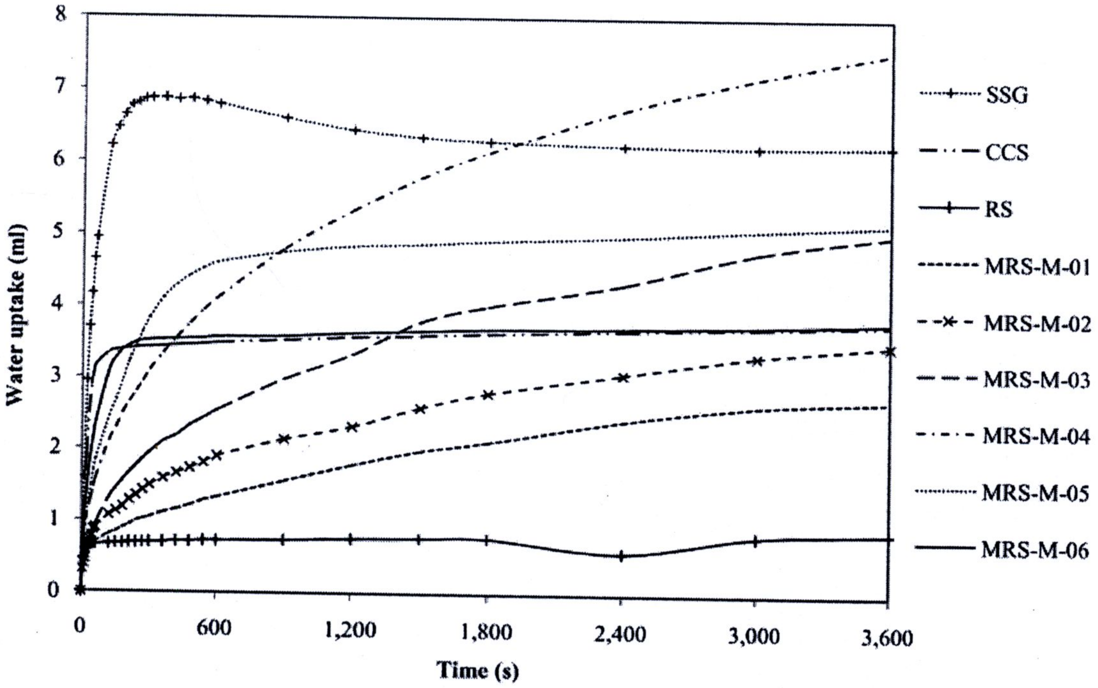


**Figure 3.25** Water uptake profiles of two commercial superdisintegrants; SSG (Explotab®) and CCS (Ac-di-sol®), native rice starch (RS) and MRS-Ms

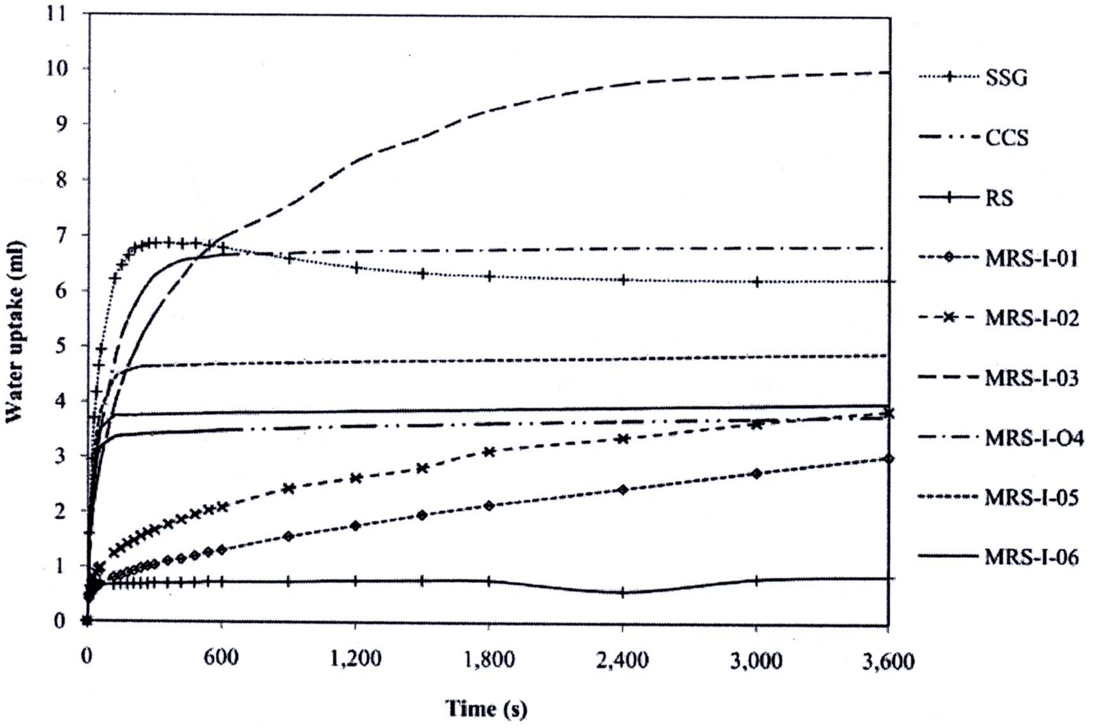


**Figure 3.26** Water uptake profiles of two commercial superdisintegrants; SSG (Explotab®) and CCS (Ac-di-sol®), native rice starch (RS) and MRS-Is

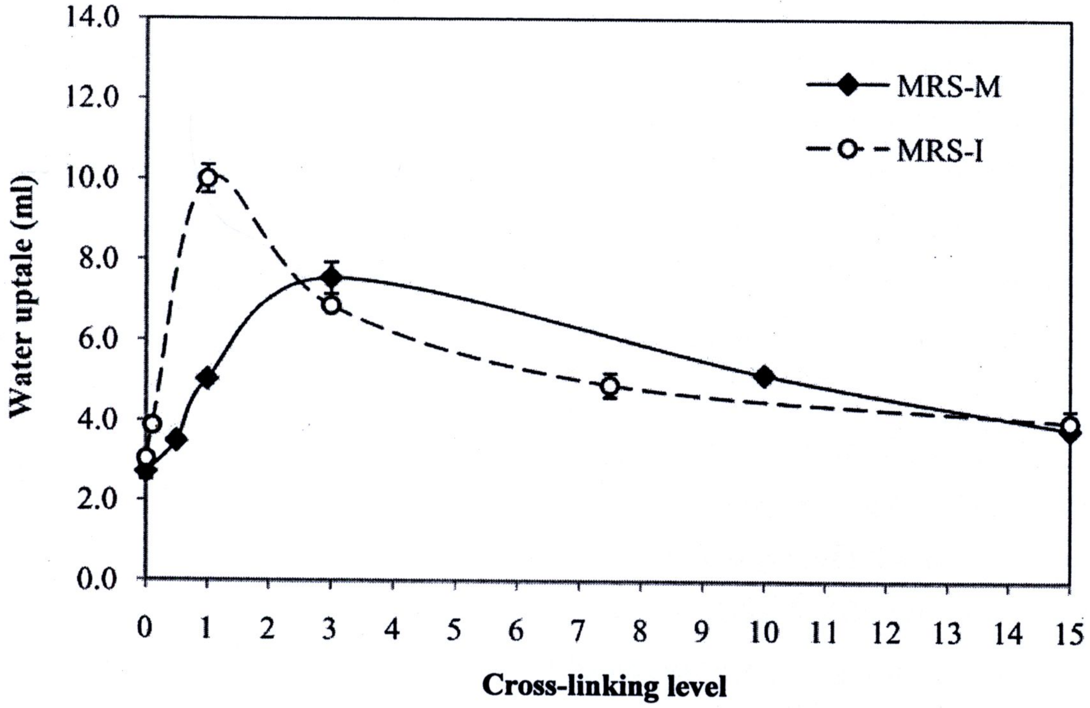


**Figure 3.27** The relationship between cross-linking level and water uptake of MRSs at 60 min

### 3.9 Flowability

Flowability is an important factor for several processes in pharmaceutical industry, including powder transfer through comparatively large equipment, powder storage, blending, fluidization and compaction process (e.g. tablet compaction). Many methods can be employed to measure the flowability of powder such as angle of repose, Hausner ratio, flow rate and compressibility ratio. In this research the flow ability of RS powder and all conditions of MRS powder was evaluated using angle of repose and compressibility ratio.

Angle of repose resembles qualitatively to flow properties of the material. It is also a direct implication of capability flowability. The repose angle of the samples was measured. Then, it is listed in table 3.3. The repose angles of RS and MRSs were in the range of 9° and 18° which was less than 25° (USP 35-NF 29). This result indicated that the flow ability of RS and MRSs was excellent. Angle of repose cannot categorize powder's characteristic; flowability test and acceptance limits are recommended to be done with empirical (Prescott and Barnum, 2000). In fact, some samples could not flow through the apparatus until they was disturbed with tapping. This is due to the polygonal shape of RS and MRS that could form the interlocking shape. This interlocking shape inhibited the flowability of the sample.

On the other hand, table 3.4 lists the bulk density, tapped density, compressibility ratio and flow ability of RS and all MRSs. From the data, the tapped density of RS was about 25% greater than the bulk density while the tapped density of MRS-M and MRS-I was between 26-33% and 19-23% greater than their bulk density. This is obvious that MRS-I showed the better flowability than RS and MRS-M. The bulk and tapped density of the powder depend on many parameters. The most significant parameters are sizes, shape and size distribution of the particles (Yotwimonwat, 1999). The results could be supported by SEM images of MRSs in previous experiment. The bigger size of conglomerated MRS-I resulted in the better flow efficiency compared with the others. The sample having higher angle of repose leaded to its decreased compressibility ratio.

**Table 3.3** Flowability of RS and MRSs determined from angle of repose

| Sample | Tan θ | Repose angle (°) | Flow |
|---|---|---|---|
| RS | 0.20 ± 0.04 | 11.30 ± 1.98 | Excellent |
| MRS-M-01 | 0.24 ± 0.02 | 13.49 ± 1.44 | Excellent |
| MRS-M-02 | 0.16 ± 0.02 | 9.09 ± 1.12 | Excellent |
| MRS-M-03 | 0.17 ± 0.00 | 9.46 ± 0.32 | Excellent |
| MRS-M-04 | 0.24 ± 0.03 | 13.85 ± 1.36 | Excellent |
| MRS-M-05 | 0.26 ± 0.02 | 14.39 ± 1.12 | Excellent |
| MRS-M-06 | 0.25 ± 0.01 | 14.03 ± 0.54 | Excellent |
| MRS-I-01 | 0.15 ± 0.00 | 8.34 ± 0.32 | Excellent |
| MRS-I-02 | 0.33 ± 0.01 | 18.43 ± 0.79 | Excellent |
| MRS-I-03 | 0.20 ± 0.02 | 11.12 ± 1.15 | Excellent |
| MRS-I-04 | 0.22 ± 0.04 | 12.39 ± 2.39 | Excellent |
| MRS-I-05 | 0.24 ± 0.03 | 13.67 ± 1.56 | Excellent |
| MRS-I-06 | 0.28 ± 0.02 | 15.82 ± 0.81 | Excellent |

**Table 3.4** Flow ability of RS and MRSs investigated from compressibility ratio

| Samples | Bulk density (g/ml) | Tapped density (g/ml) | Compressibility Ratio (%) | Flow |
|---|---|---|---|---|
| RS | 0.45 ± 0.00 | 0.60 ± 0.00 | 25.44 ± 0.43 | Poor |
| MRS-M-01 | 0.50 ± 0.00 | 0.67 ± 0.00 | 25.78 ± 0.55 | Poor |
| MRS-M-02 | 0.42 ± 0.01 | 0.61 ± 0.00 | 31.17 ± 0.90 | Poor |
| MRS-M-03 | 0.42 ± 0.00 | 0.63 ± 0.00 | 32.59 ± 0.36 | Poor |
| MRS-M-04 | 0.44 ± 0.01 | 0.60 ± 0.00 | 25.86 ± 1.32 | Poor |
| MRS-M-05 | 0.41 ± 0.01 | 0.60 ± 0.00 | 31.11 ± 1.00 | Poor |
| MRS-M-06 | 0.42 ± 0.00 | 0.62 ± 0.00 | 33.09 ± 0.87 | Poor |
| MRS-I-01 | 0.43 ± 0.02 | 0.53 ± 0.02 | 19.16 ± 1.16 | Fair to passable |
| MRS-I-02 | 0.43 ± 0.01 | 0.53 ± 0.00 | 18.78 ± 0.44 | Fair to passable |
| MRS-I-03 | 0.42 ± 0.00 | 0.54 ± 0.00 | 21.88 ± 0.94 | Fair to passable |
| MRS-I-04 | 0.42 ± 0.00 | 0.55 ± 0.00 | 23.40 ± 0.42 | Poor |
| MRS-I-05 | 0.39 ± 0.01 | 0.48 ± 0.00 | 20.20 ± 0.93 | Fair to passable |
| MRS-I-06 | 0.37 ± 0.01 | 0.49 ± 0.00 | 23.33 ± 0.76 | Poor |

## 3.10 Pressure-hardness profile

The characterization of pharmaceutical powder compressibility plays an important role in the manufacturing of tablets. Good compressible powder must provide high tablet hardness under less applied pressure. The relationships between compressing pressure and the hardness of tablets (Pressure-hardness profiles) are shown in Figure 3.28-3.32. The graph of all starch samples was shown in linear regressive trend. The linear regression was utilized to analyze the correlation between compression force and tablet hardness. The parameters (slope and linear correlation) obtained from the linear regression of each condition of tablet are listed in table 3.5. The slope of RS was 9.48, while the slope of MRS-M and MRS-I were in range of 9.33 to 14.21 and 7.18 to 10.33, respectively. A higher slope in pressure-hardness profile indicates a better compressibility of powder. This is obvious that most of MRS-M showed better compressibility than RS and MRS-I. The range of hardness of the tablets obtained under the upper-pressure at 0.5-3.0 ton (hardness$_{0.5\text{-}3T}$) was correlated with slope from the graph. The higher slope providing sample also displayed higher hardness$_{0.5\text{-}3T}$.

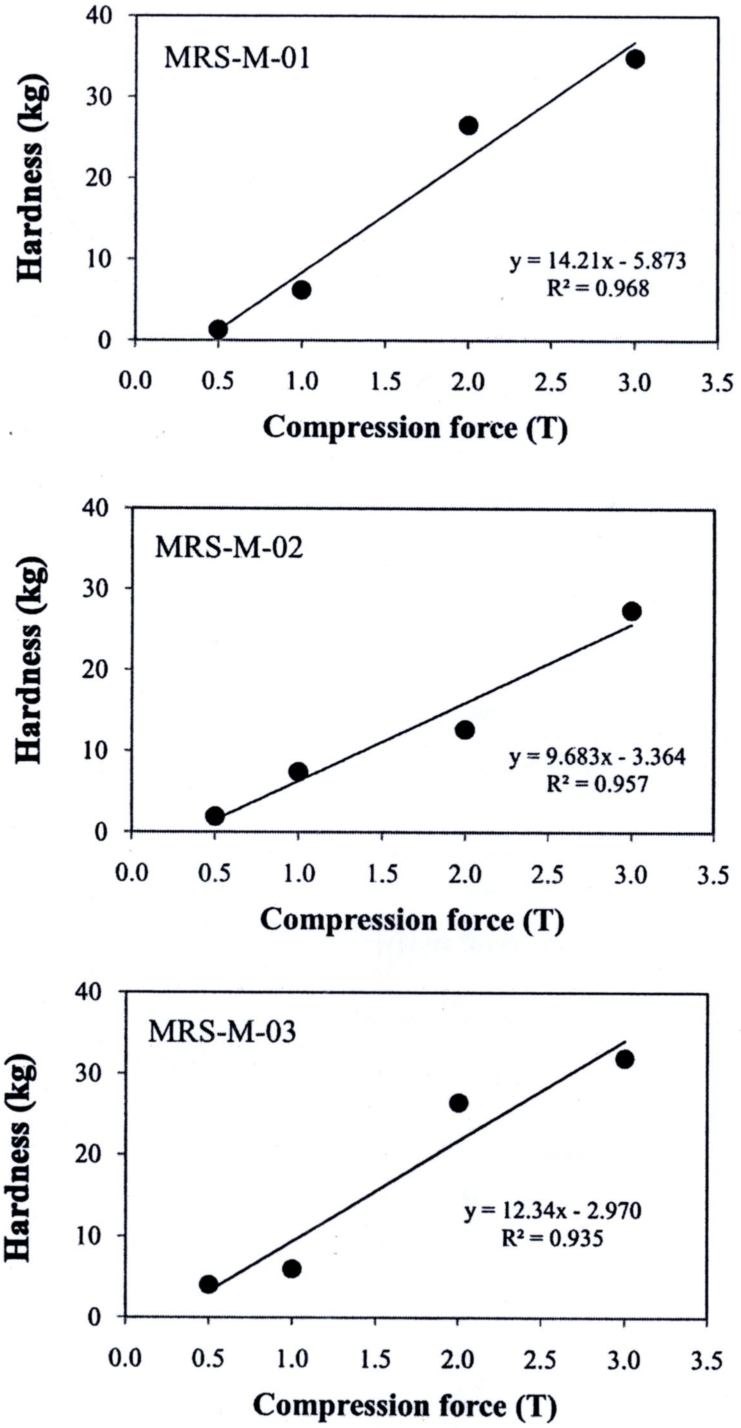


**Figure 3.28** Pressure-hardness profile of modified rice starches in different conditions: MRS-M-01, MRS-M-02 and MRS-M-03

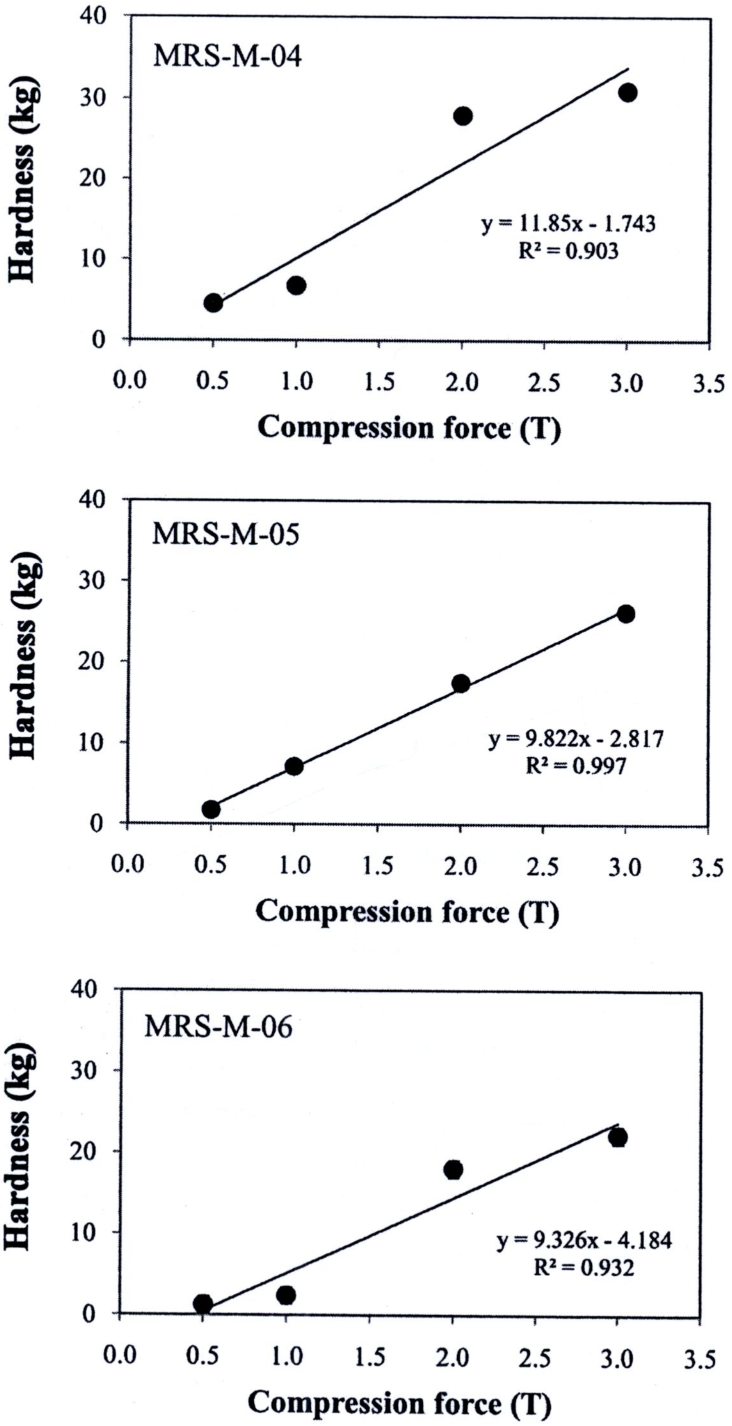


**Figure 3.29** Pressure-hardness profile of modified rice starches in different conditions: MRS-M-04, MRS-M-05 and MRS-M-06

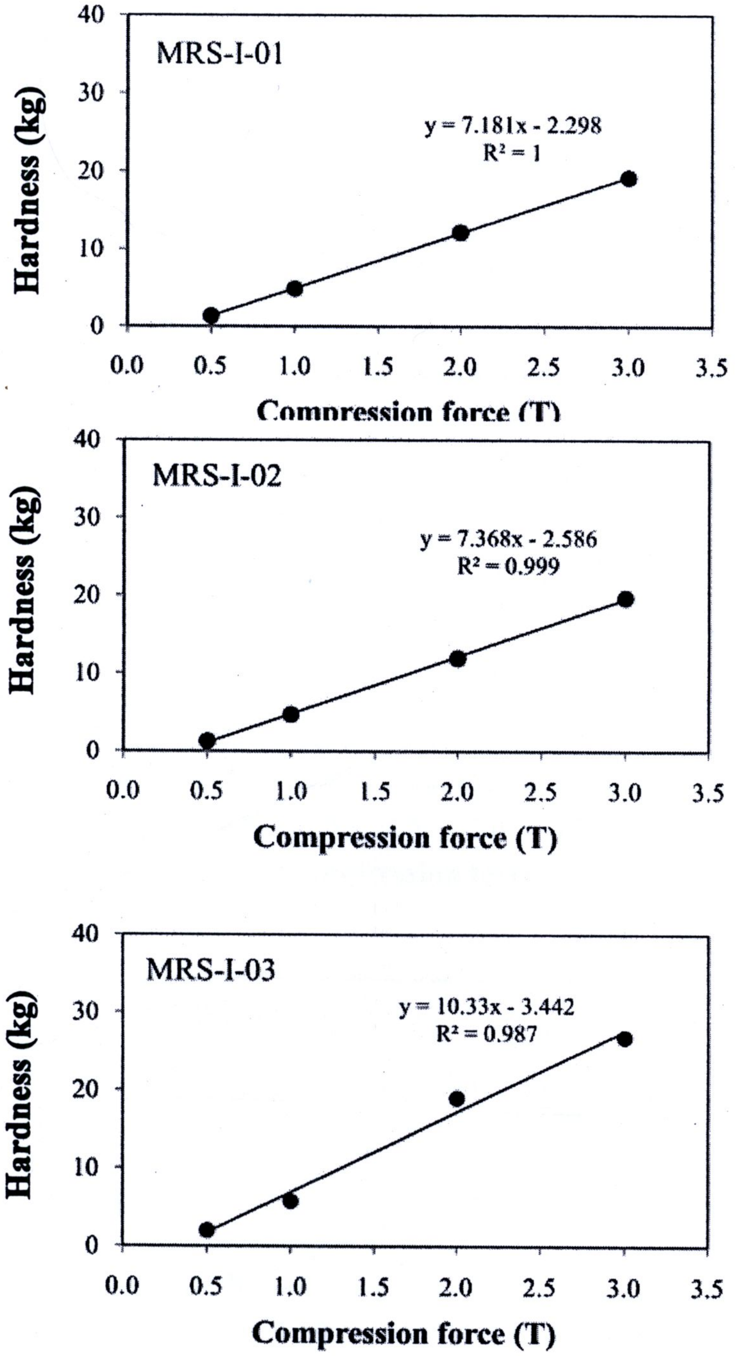


**Figure 3.30** Pressure-hardness profile of modified rice starches in different conditions: MRS-I-01, MRS-I-02 and MRS-I-03

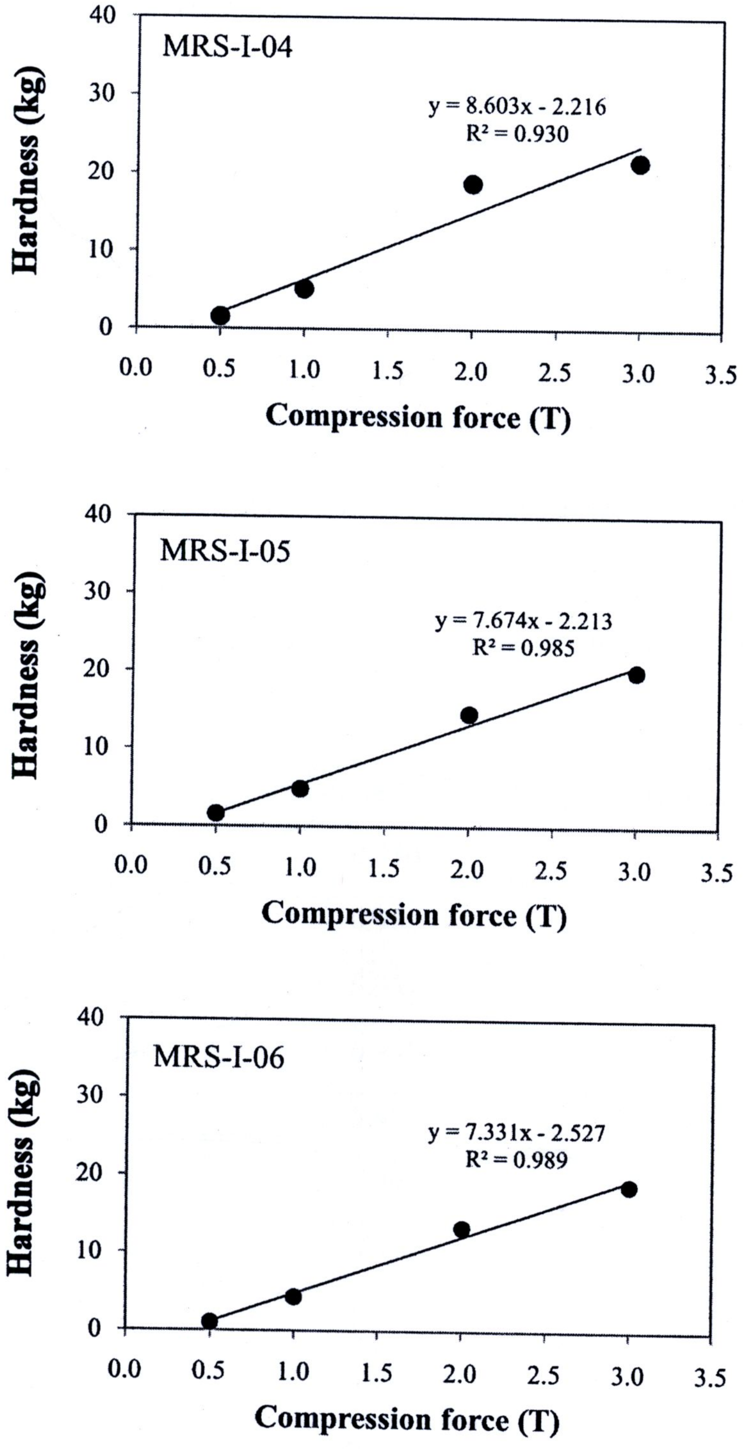


**Figure 3.31** Pressure-hardness profile of modified rice starches in different conditions: (a) MRS-I-04, (b) MRS-I-05 and (c) MRS-I-06

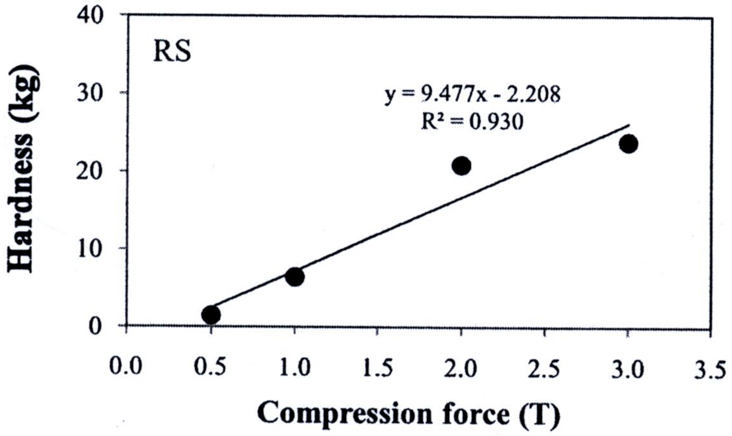


**Figure 3.32** Pressure-hardness profile of native rice starch

**Table 3.5** The parameters obtained from linear regression analysis between compression force and tablet hardness.

| Samples | Slope | Correlation coefficient | Hardness at 0.5-3 T |
|---|---|---|---|
| RS | 9.477 | 0.930 | 1.48±0.04 - 23.87±1.79 |
| MRS-M-01 | 14.210 | 0.968 | 1.33±0.05 - 34.81±1.30 |
| MRS-M-02 | 9.683 | 0.957 | 1.89±0.04 - 27.43±1.46 |
| MRS-M-03 | 12.340 | 0.935 | 4.02±0.13 - 31.91±0.24 |
| MRS-M-04 | 11.850 | 0.903 | 4.52±0.35 - 30.93±0.77 |
| MRS-M-05 | 9.822 | 0.997 | 1.73±0.18 - 26.21±0.84 |
| MRS-M-06 | 9.326 | 0.932 | 1.25±0.43 - 22.21±0.70 |
| MRS-I-01 | 7.181 | 1.000 | 1.29±0.05 - 19.22±0.92 |
| MRS-I-02 | 7.360 | 0.999 | 1.25±0.06 - 19.68±0.49 |
| MRS-I-03 | 10.330 | 0.987 | 1.98±0.04 - 26.75±2.53 |
| MRS-I-04 | 8.603 | 0.930 | 1.54±0.04 - 21.56±1.46 |
| MRS-I-05 | 7.674 | 0.985 | 1.56±0.07 - 20.07±0.72 |
| MRS-I-06 | 7.331 | 0.989 | 1.06±0.06 - 18.83±0.25 |

The results from previous experiments, especially the water uptake profile, indicated a possible use of modified starches as pharmaceutical excipient, a tablet disintegrant. Therefore, some MRSs such as MRS-03, MRS-04, MRS-05, MRS-06, MRS-I-03, MRS-I-04, MRS-I-05, and MRS-I-06 were chosen to study their pharmaceutical potential as tablet disintegrant by using aspirin as a model drug and silicified microcrystalline cellulose (SMCC) as a diluent. First, the SMCC tablets (705.71 mg) containing various types of 2% disintegrants (RS, MRSs, and two commercial superdisintegrants; sodium starch glycolate (SSG) and croscarmellose sodium (CCS)) were prepared and evaluated. The tests for determination of disintegration time (DT), wetting time (WT) and water adsorption ratio (R) were the required experiments. In addition, the aspirin tablet (712.60 mg) containing 500 mg aspirin and several types and amounts (2-6%) of disintegrants (RS, MRSs, SSG, and CCS) using SMCC as filler were also prepared and studied.

## 3.11 The study of MRS as disintegrant in SMCC tablets

### 3.11.1 Tablet preparation

SMCC tablets (705.71 mg) containing different types of 2% disintegrants (RS, MRSs and two commercial superdisintegrant: SSG and CCS) were direct compressed with a single punch press. The appearance of SMCC tablets containing MRS-M-04 as a disintegrant is presented in Figure 3.33. The other conditions of SMCC tablet showed the same appearance (data not shown).

The coefficient of variation (CV) for weight of tablet, thickness, friability, and hardness of SMCC tablets were measured. The results are shown in Table 3.6. The CV for weight of SMCC tablets was within the range of 0.30-1.22 % (USP 34-NF 29). Thickness of the tablets ranged between 0.242-0.243 inches while the hardness was in the range of 11.85-13.74 kg that acceptable (USP 34-NF 29). Friability of the tablets was less than 1.0% (USP 34-NF 29) and it was negative because of moisture absorption during testing.

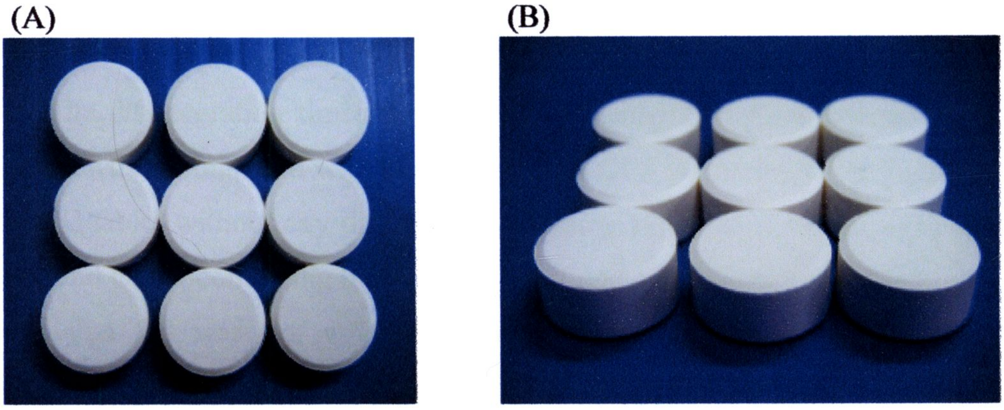


**Figure 3.33** Appearance of SMCC tablets containing MRS-M-04 as a disintegrant; (A) top view, and (B) side view

**Table 3.6** Quality control of SMCC tablets containing various types of disintegrant

| Types of disintegrants | CV for weight (%) | Thickness (inch) | Friability (%) | Hardness (kg) |
|---|---|---|---|---|
| none | 0.96 | 0.2429±0.0001 | -0.34±0.03 | 12.42±0.53 |
| SSG | 0.79 | 0.2429±0.0003 | -0.31±0.01 | 13.26±0.32 |
| CCS | 0.30 | 0.2429±0.0002 | -0.20±0.02 | 12.53±0.54 |
| RS | 1.22 | 0.2431±0.0003 | -0.26±0.03 | 11.85±0.52 |
| MRS-M-03 | 0.99 | 0.2423±0.0001 | -0.32±0.01 | 13.74±0.29 |
| MRS-M-04 | 0.96 | 0.2428±0.0001 | -0.27±0.01 | 13.10±0.35 |
| MRS-M-05 | 0.81 | 0.2427±0.0002 | -0.29±0.03 | 13.21±0.21 |
| MRS-M-06 | 0.51 | 0.2423±0.0002 | -0.33±0.01 | 13.19±0.43 |
| MRS-I-03 | 1.11 | 0.2428±0.0002 | -0.31±0.01 | 12.43±0.30 |
| MRS-I-04 | 0.44 | 0.2426±0.0001 | -0.32±0.01 | 12.63±0.39 |
| MRS-I-05 | 0.54 | 0.2428±0.0001 | -0.26±0.03 | 12.57±0.48 |
| MRS-I-06 | 0.58 | 0.2428±0.0002 | -0.37±0.03 | 12.53±0.39 |

### 3.11.2 Disintegration time (DT), Wetting time (WT), and water absorption ratio (R)

The disintegration times (DT) of SMCC tablet containing several types of 2% RS and MRSs compared with that of SSG and CCS are presented in Figure 3.34. The SMCC tablet without any disintegrants disintegrated within 17 sec. The DT of RS, SSG and CCS –containing tablets were 18, 2 and 4 sec, respectively. The results indicated that RS was not effective enough to be a good disintegrant in this concentration for SMCC tablet. The similar result was previously reported for native rice starch by Kittipongpatana et al. (2010). They, however, found that native rice starch showed curtain degree of disintegrating capability at a higher concentration. Tablets containing all types of MRSs disintegrated within range between 3 and 9 sec, except that of MRS-M-03 which exhibited the lowest disintegration (within 26 sec). This phenomenon demonstrated that all MRSs, except MRS-M-03, possessed disintegrant properties. Due to MRS-M-03 could form gel when it was touched with water (from lowering level of cross-linking), although it had highest swellability (Figure 3.5), it was not suitable to use as a tablet disintegrating agent. The fastest disintegration was obtained from tablet composing MRS-I-03 as only in 3 sec, which is also lower than that of CCS but until higher than that of SSG (2 sec).

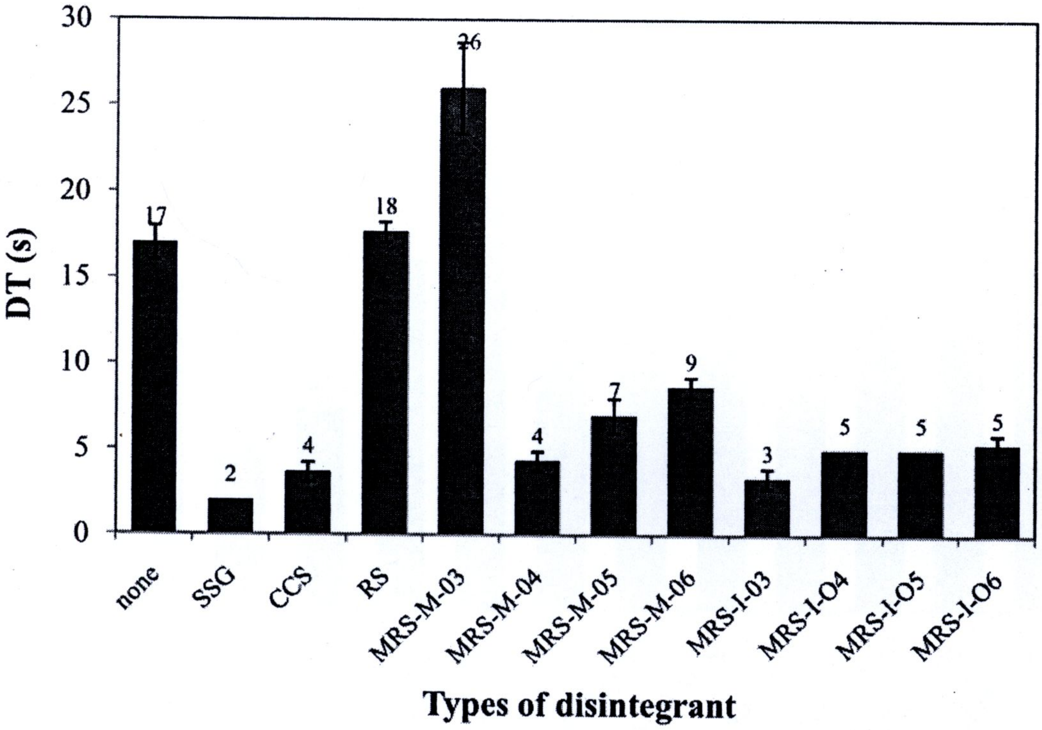


**Figure 3.34** Disintegration time (DT) of SMCC tablet containing several types of 2% disintegrant

Wetting time (WT) of dosage form is associated to the contact angle and it is used to evaluate disintegration properties of the tablets. The lower WT indicates an decreasing in disintegration time of the tablet (Hirani et al., 2009). The WT testing utilizes minimal water unlike the disintegration test. The WT of SMCC tablet composing various types of 2% RS and MRSs compared with that of SSG and CCS is shown in Figure 3.35. The WT of tablet without disintegrating agent was 102 sec. The SMCC tablet containing RS, SSG and CCS provided the WT as within 108, 51 and 62 sec, respectively. MRS-M-03 and MRS-I-03 provided the slowest (150 sec) and fastest (66 sec) time for wetting of the SMCC tablet, respectively. The tablets composing the other MRSs showed WT in range of 81-99 sec. In addition, the WT value of SMCC tablets from this study exhibited the correlated trend with DT value presented and explained above. The DT and WT value was correlated with water uptake of MRS as a tablet disintegrant. Faster DT and WT were obtained from the tablet composing higher water uptake MRS.

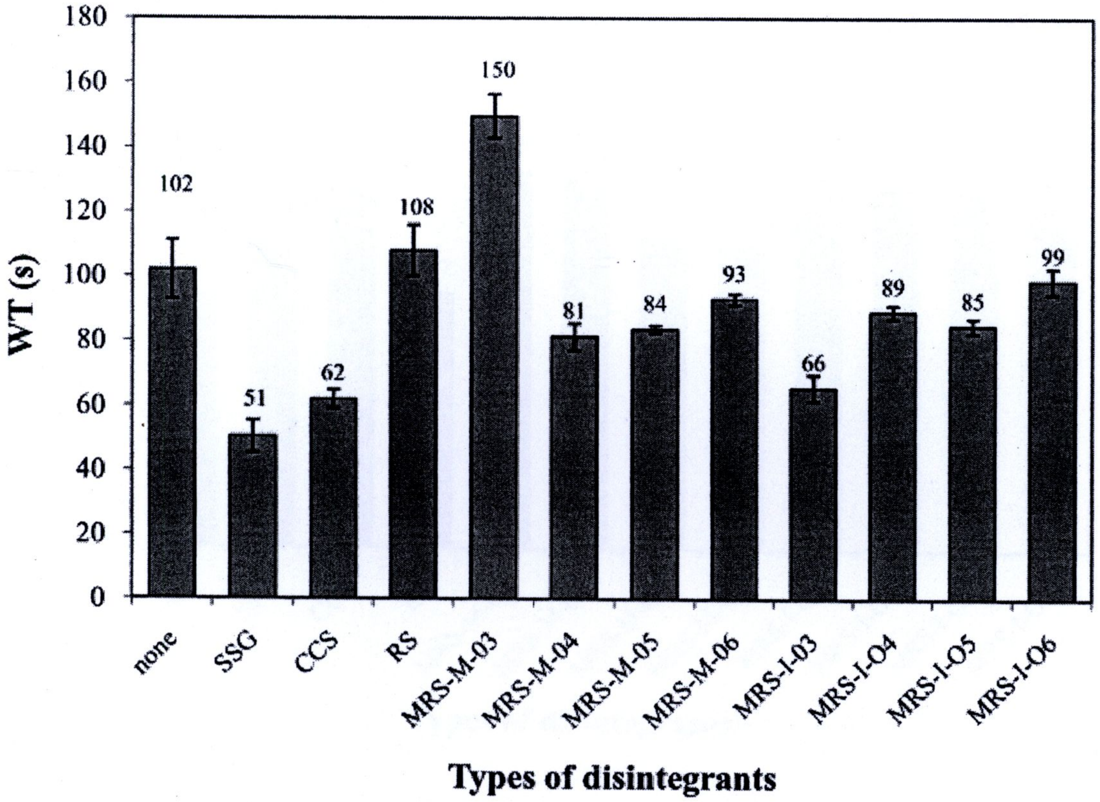


**Figure 3.35** Wetting time (WT) of SMCC tablet

Water absorption ratio (R) was calculated from the difference between weight of tablet before ($W_A$) and after wetting ($W_B$), and then divided with the $W_A$ (described as Equation 2.21. The R value of SMCC tablets with different types of disintegrants (2%) is shown in Figure 3.36. The tablets carrying none disintegrant and 2% RS gave the same value of R as 0.97. This mean 2% RS did not possess water absorption property as previously described in the part of water uptake experiment. In this term, tablet carrying 2% MRS-I-04 gave higher R value (1.50) compared to that of the other MRSs and CCS, and it was comparable to that of SSG. Interestingly, the trend of R value of tablet containing 2% MRSs was related with swelling volume value in prior testing. The MRS that had higher swellability would also exhibit the higher R value.

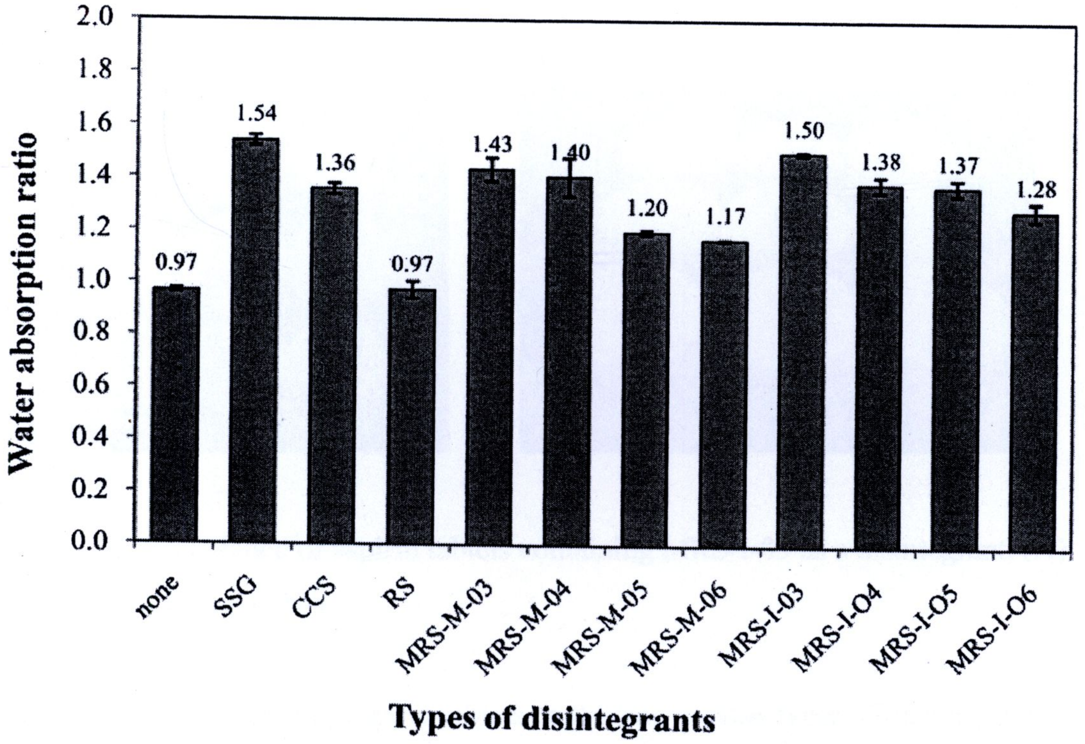


**Figure 3.36** Water absorption ratio (R) of SMCC tablet

## 3.12 The study of MRSs as disintegrant in aspirin tablets

### 3.12.1 Tablet preparation

The aspirin tablets (712.60 mg) were prepared by direct compression using a single punch press. Each tablets carried various types of 2% disintegrants such as RS, MRSs, SSG and CCS, resemble in the previous experiment for SMCC tablets. The appearance of aspirin tablets containing MRS-I-03 as a disintegrant is presented in Figure 3.31. The other tablets containing separated disintegrants were presented the same appearance (data not shown).

Table 3.7 lists the CV for weight of tablet, thickness, friability, and hardness of aspirin tablets. The CV for weight of the tablets was between 0.49-1.21% (USP 34-NF 29). Thickness of the tablets was within the range of 0.186-0.187 inches while the hardness was in the range of 8.81-11.04 that acceptable (USP 34-NF 29). Friability of the tablets was less than 1.0% (USP 34-NF 29) and it was negative same as that of SMCC tablets.

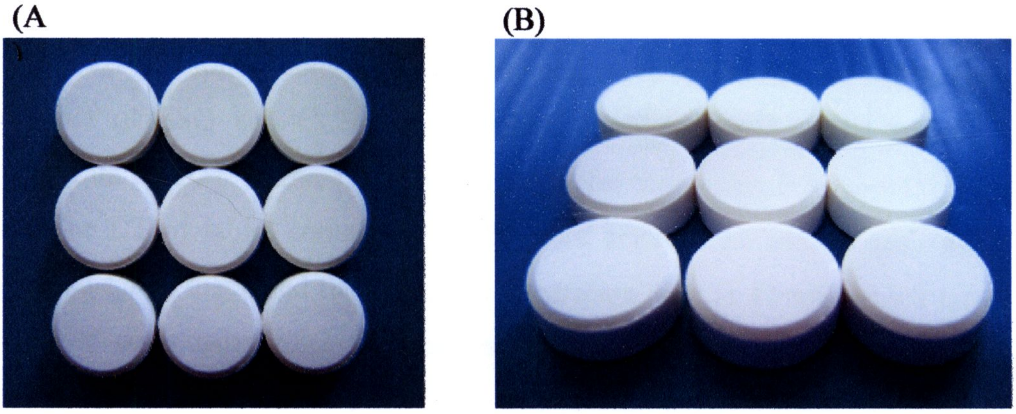


**Figure 3.37** Appearance of aspirin tablets containing MRS-I-03 as a disintegrant; (A) top view, and (B) side view

**Table 3.7** Quality control of aspirin tablets containing various types of disintegrant

| Types of disintegrants | CV for weight of tablet (%) | Thickness (inch) | Friability (%) | Hardness (kg) |
|---|---|---|---|---|
| none | 0.66 | 0.1862±0.0018 | 0.29±0.05 | 8.97±0.33 |
| SSG | 1.08 | 0.1869±0.0009 | 0.45±0.06 | 11.04±0.60 |
| CCS | 0.49 | 0.1867±0.0009 | 0.42±0.07 | 9.92±0.59 |
| RS | 1.04 | 0.1865±0.0013 | 0.24±0.07 | 10.52±0.66 |
| MRS-M-03 | 0.80 | 0.1867±0.0010 | 0.22±0.22 | 10.09±0.53 |
| MRS-M-04 | 0.51 | 0.1866±0.0010 | 0.44±0.05 | 10.14±0.43 |
| MRS-M-05 | 0.86 | 0.1871±0.0006 | 0.39±0.01 | 10.12±0.63 |
| MRS-M-06 | 0.53 | 0.1868±0.0010 | 0.44±0.07 | 10.02±0.46 |
| MRS-I-03 | 0.84 | 0.1871±0.0006 | 0.40±0.07 | 9.88±0.44 |
| MRS-I-04 | 1.21 | 0.1865±0.0010 | 0.19±0.02 | 9.87±0.28 |
| MRS-I-05 | 0.68 | 0.1863±0.0014 | 0.36±0.05 | 9.95±0.51 |
| MRS-I-06 | 0.51 | 0.1867±0.0008 | 0.17±0.05 | 8.81±0.46 |

### 3.12.2 Disintegration time (DT), Wetting time (WT), and water absorption ratio (R)

DT of aspirin tablet containing several types of 2% RS and MRSs compared with that of SSG and CCS was presented in Figure 3.38. The tablet without disintegrant had DT within 79 sec while the tablet composing RS show DT within 39 sec. The DT of tablet containing MRSs were between 11 and 26 sec. MRS-I-05 contained tablet displayed the fastest disintegration only in 11 sec, which faster than the tablet composing SSG (21 sec) and CCS (19 sec) about 2 and 1.7 times, respectively. The results indicated that 2% of each MRS could be used as a tablet disintegrant for aspirin.

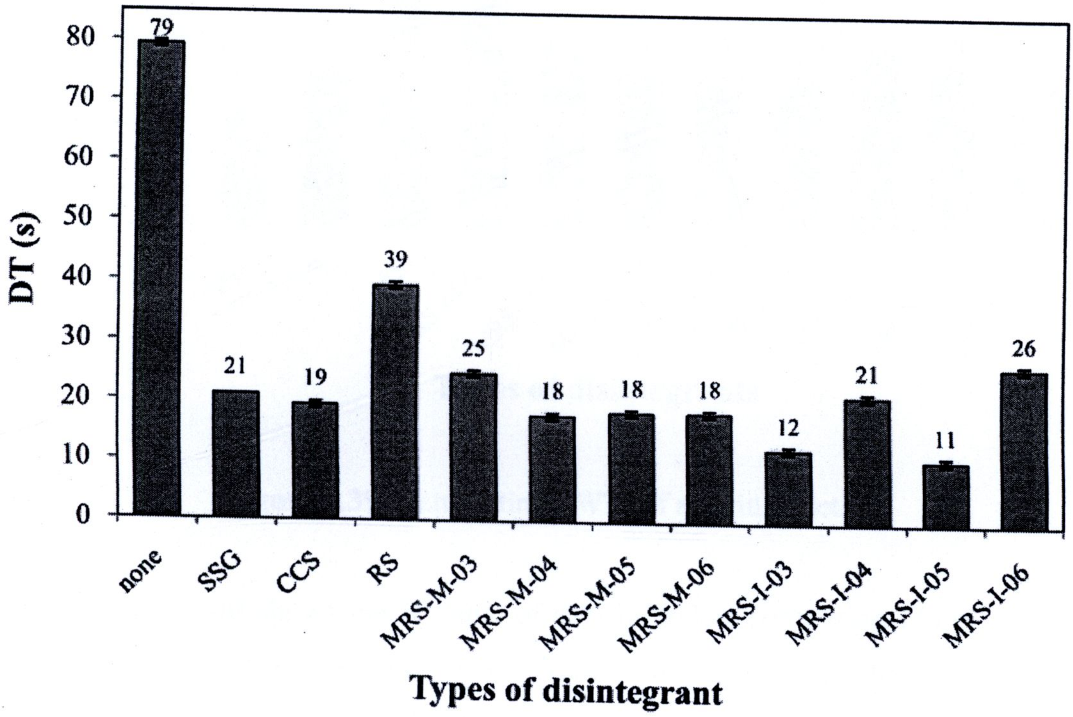


**Figure 3.38** Disintegration time (DT) of aspirin tablet containing several types of 2% disintegrant

Figure 3.39 presented the WT of aspirin tablet containing 2% of different disintegrants (RS, MRSs, SSG and CCS). The WT of aspirin tablet without disintegrant was the highest at 95 sec while the tablet composing RS provided the WT at 77 sec. SSG composed tablets showed the lowest WT (40 sec) compared with others. The tablets containing the MRSs showed WT in the range of 46-58 sec. The fastest WT was found from MRS-I-03 composed tablet (46 sec), which was also lower than that of CCS (48 sec) but higher than that of SSG. These results were similar to WT for SMCC tablets described in previous experiment.

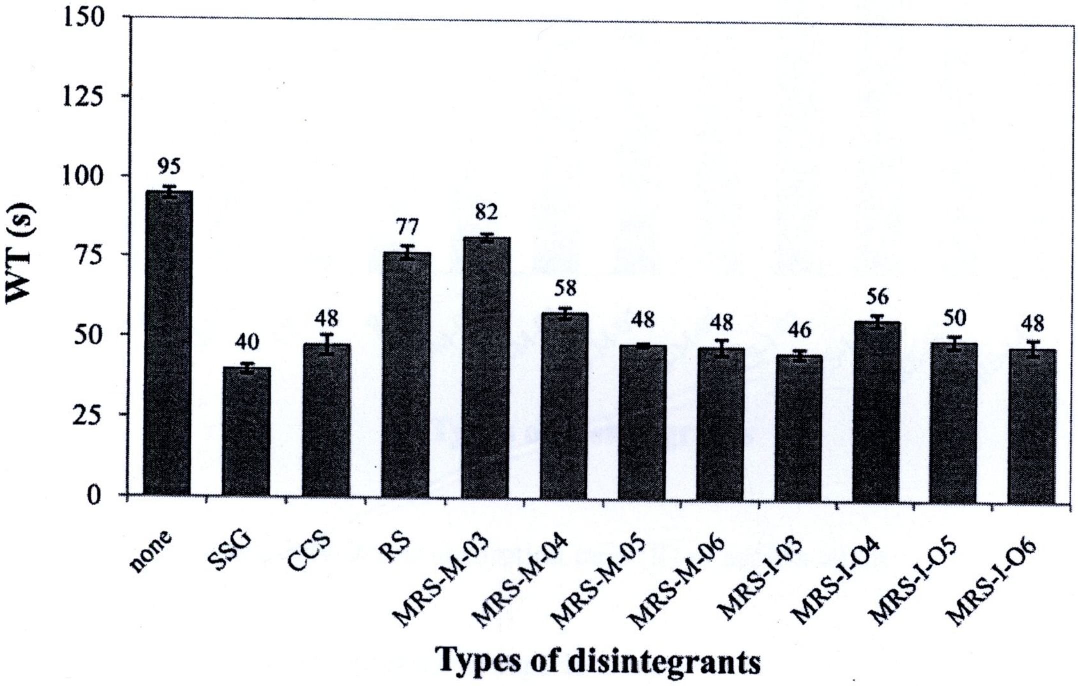


**Figure 3.39** Wetting time (WT) of aspirin tablet

Figure 3.40 shows the R value of aspirin tablets composing 2% of several disintegrants (RS, MRSs, SSG and CCS). The tablets carrying none disintegrant gave the value of R at 0.33. The R value from RS-carrying tablet (0.47) was small higher than that of none-disintegrant. The tablet containing 2% of MRS-I-04 gave higher R value (0.76) than that of the other MRSs and CCS, but it until slightly lower than that of SSG (0.78). These observations were similarly to R value of MRS-containing SMCC tablets which presented previously. The trend of R value of aspirin tablet carrying 2% MRSs was also correlated with swelling volume value in prior testing. Then, the MRS that had higher swelling volume value would also display the higher R value.

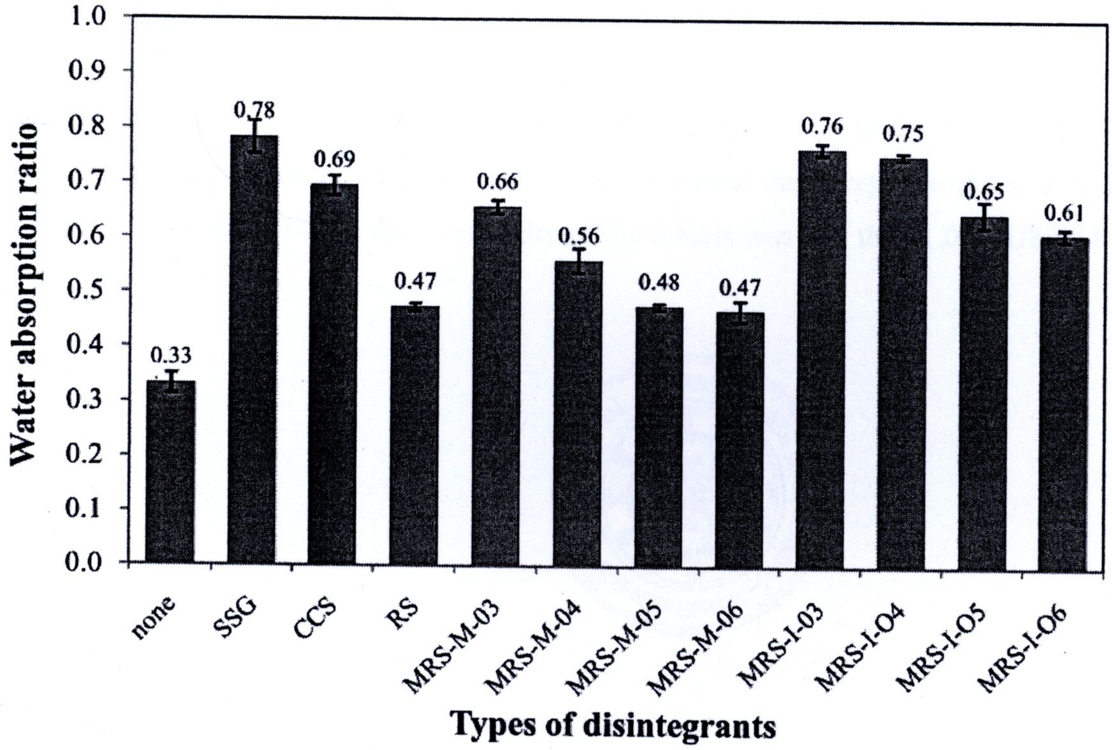


**Figure 3.40** Water absorption ratio (R) of aspirin tablet

## 3.13 The effect of MRSs content in aspirin tablets

### 3.13.1 Tablet preparation

The effect of several types and concentrations of disintegrants on disintegration of aspirin tablet was investigated. In this study, some modified rice starches (e.g. MRS-M-03, MRS-I-04, and MRS-I-15) were used as a tablet disintegrant comparing with RS, SSG and CCS. MRS-M-03, MRS-I-04, and MRS-I-15 showed the obviously different swellability as previously shown in the Figure 3.5, they presented a highest, middle and lowest capacity of swelling, respectively. The aspirin tablets (700 mg) were prepared by direct compression using a single punch press. Each tablets carried various types and concentrations (2-6% w/w) of disintegrants such as RS, MRSs and two commercial superdisintegrants (SSG and CCS). Each aspirin tablet presented the same appearance (data not shown) and similar to that of the aspirin tablets in the Figure 3.7. All tablets were quality controlled before analysis. Table 3.8 and 3.9 show the results of quality for the CV for weight of tablet, thickness, friability, and hardness of aspirin tablets. The CV for weight of the tablets was between 0.51-2.12% (USP 34-NF 29). Thickness of the tablets was in the range of 0.186-0.187 inches while the hardness ranged between 9.62 and 11.25. The variations of both parameters are within the acceptable range of the Pharmacopeia (USP 34-NF 29). Friability of the tablets was less than 1.0% (USP 34-NF 29).

**Table 3.8** Weight variation, thickness, friability and hardness of aspirin tablets containing various types (SSG, CCS, and RS) and amounts (2-6%) of disintegrants

| Types of disintegrants | Disintegrant content (%) | CV for weight (%) | Thickness (inch) | Friability (%) | Hardness (kg) |
|---|---|---|---|---|---|
| SSG | 2 | 1.08 | 0.1864±0.0012 | 0.45±0.06 | 11.04±0.6 |
| | 3 | 0.99 | 0.1868±0.0010 | 0.50±0.06 | 11.25±0.34 |
| | 4 | 1.98 | 0.1866±0.0009 | 0.44±0.01 | 10.94±0.55 |
| | 5 | 2.06 | 0.1867±0.0009 | 0.61±0.03 | 10.41±0.86 |
| | 6 | 1.37 | 0.1866±0.0009 | 0.59±0.01 | 10.16±0.51 |
| CCS | 2 | 0.51 | 0.1862±0.0012 | 0.42±0.07 | 9.92±0.59 |
| | 3 | 0.91 | 0.1871±0.0006 | 0.40±0.05 | 10.89±0.53 |
| | 4 | 0.92 | 0.1868±0.0010 | 0.48±0.05 | 10.19±0.47 |
| | 5 | 0.69 | 0.1867±0.0008 | 0.52±0.01 | 9.62±0.32 |
| | 6 | 1.20 | 0.1862±0.0009 | 0.49±0.03 | 9.86±0.52 |
| RS | 2 | 1.04 | 0.1863±0.0012 | 0.24±0.07 | 10.52±0.66 |
| | 3 | 0.69 | 0.1864±0.0009 | 0.25±0.05 | 11.02±0.54 |
| | 4 | 0.82 | 0.1866±0.0010 | 0.29±0.04 | 11.06±0.60 |
| | 5 | 0.90 | 0.1868±0.0008 | 0.35±0.03 | 9.65±0.34 |
| | 6 | 0.73 | 0.1866±0.0009 | 0.31±0.06 | 11.01±0.55 |

**Table 3.9** Weight variation, thickness, friability and hardness of aspirin tablets containing various types and concentrations (2-6%) of modified rice starch as tablet disintegrant

| Types of disintegrants | Disintegrant content (%) | CV for weight (%) | Thickness (inch) | Friability (%) | Hardness (kg) |
|---|---|---|---|---|---|
| MRS-M-03 | 2 | 0.80 | 0.1864±0.0012 | 0.22±0.22 | 10.09±0.53 |
| | 3 | 1.75 | 0.1868±0.0010 | 0.33±0.06 | 9.86±0.50 |
| | 4 | 2.12 | 0.1870±0.0005 | 0.44±0.05 | 10.32±0.72 |
| | 5 | 1.51 | 0.1863±0.0009 | 0.46±0.02 | 9.96±0.66 |
| | 6 | 1.95 | 0.1865±0.0013 | 0.53±0.06 | 10.22±0.36 |
| MRS-I-04 | 2 | 1.21 | 0.1864±0.0009 | 0.19±0.02 | 9.87±0.28 |
| | 3 | 1.07 | 0.1865±0.0010 | 0.30±0.01 | 10.08±0.52 |
| | 4 | 1.16 | 0.1869±0.0007 | 0.25±0.01 | 10.00±0.44 |
| | 5 | 1.05 | 0.1870±0.0006 | 0.32±0.01 | 9.87±0.48 |
| | 6 | 0.71 | 0.1863±0.0010 | 0.34±0.02 | 10.31±0.43 |
| MRS-I-06 | 2 | 0.51 | 0.1866±0.0013 | 0.17±0.05 | 8.81±0.46 |
| | 3 | 1.77 | 0.1868±0.0007 | 0.31±0.01 | 9.85±0.64 |
| | 4 | 0.72 | 0.1869±0.0008 | 0.28±0.03 | 9.66±0.43 |
| | 5 | 1.66 | 0.1869±0.0007 | 0.30±0.03 | 9.94±0.60 |
| | 6 | 0.76 | 0.1864±0.0010 | 0.29±0.02 | 9.64±0.53 |

### 3.13.2 Disintegration time (DT), Wetting time (WT), and water absorption ratio (R)

The effect of disintegrating agent concentration on the disintegration time (DT) of aspirin tablets is shown in Figure 3.41. When the proportion of disintegrants was increased the disintegration time declined as expected for aspirin tablet containing RS. In contrast, the DT increased with increase of concentration of MRS-M-03. This is because of its gel mass formed during disintegrating exhibit as a sustainer for tablet from the water outside. Nattapulwat et al. (2008) reported that viscous or gel mass was observed when carboxymethyl starch was suspended in water high concentrations (9-15%). In addition, Kittipongpatana et al. (2007) found that the solubility and viscosity properties of carboxymethyl rice starch were explainable for the tablet-binding properties and it was not appropriate to use as a tablet disintegrant. For MRS-I-04 and MRS-I-06 –containing tablets, the higher proportion of MRS affected the DT of tablet was slightly decreased. Moreover, the DT of tablet seemed to be not affected by SSG and CCS concentration.

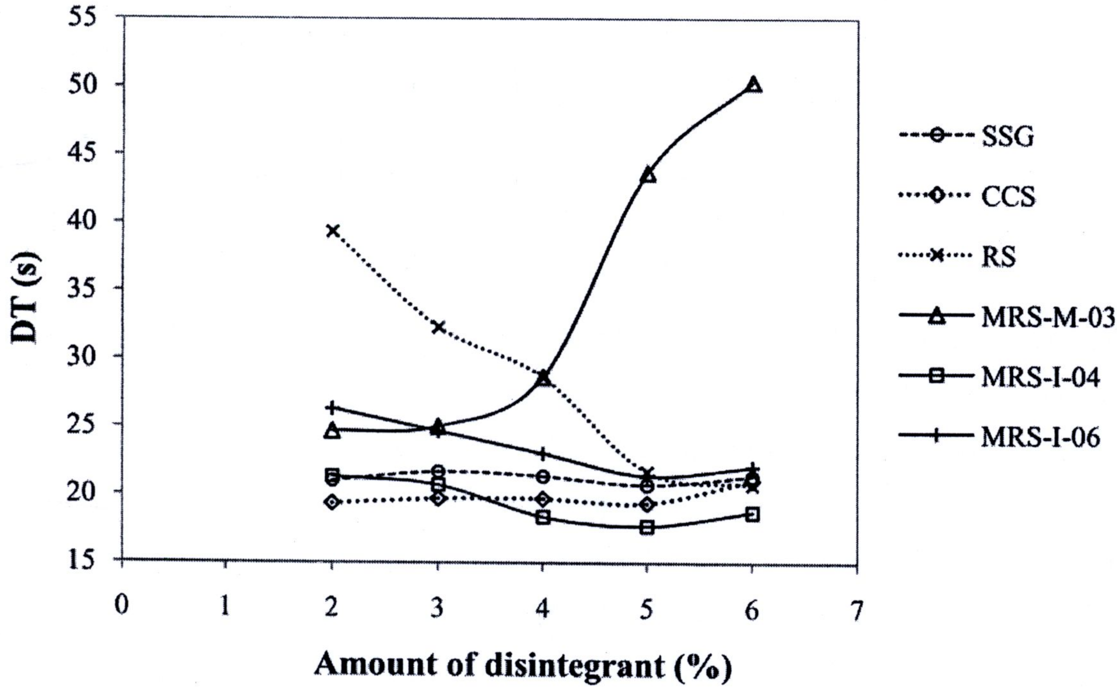


**Figure 3.41** Disintegration time (DT) of aspirin tablets containing various contents of disintegrant

The relationship between disintegrant proportions and WT of aspirin tablet is presented in Figure 3.42. The WT of tablet gradually decreased when the concentration of RS was increased while increase of concentration of MRS-M-03 could cause the WT of tablet increased. In this study, the slightly decrease of the WT for tablet containing higher MRS-I-06 was happened. Then, SSG and CCS proportion was not influenced the WT of tablet.

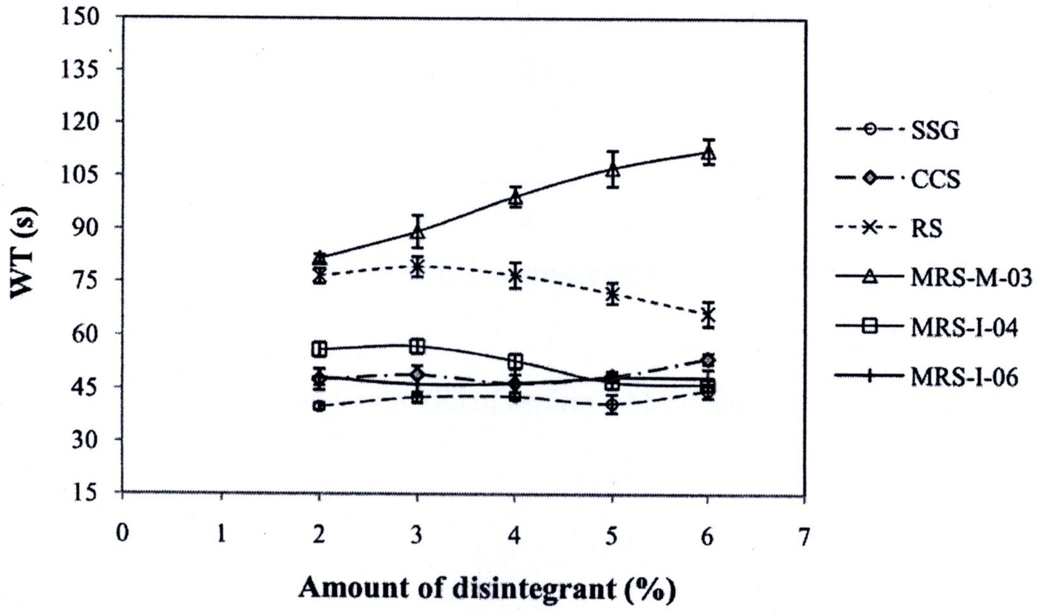


**Figure 3.42** Wetting time (WT) of aspirin tablet containing various amounts of disintegrating agents

The R value of aspirin tablets containing various types and content of disintegrant is shown in Figure 3.42. The R value of the tablets is increase according to increasing in amount of disintegrant. The tablet containing RS exhibited the lowest R value compared with that of the others in each disintegrant concentration while MRS-M-03 provided the lower R value than MRS-I-04 and MRS-I-06. Among all MRS composed tablets, MRS-I-04 and MRS-I-06 gave the R value which comparable to SSG at 3-5%, although it was until lower at 2 and 6%.

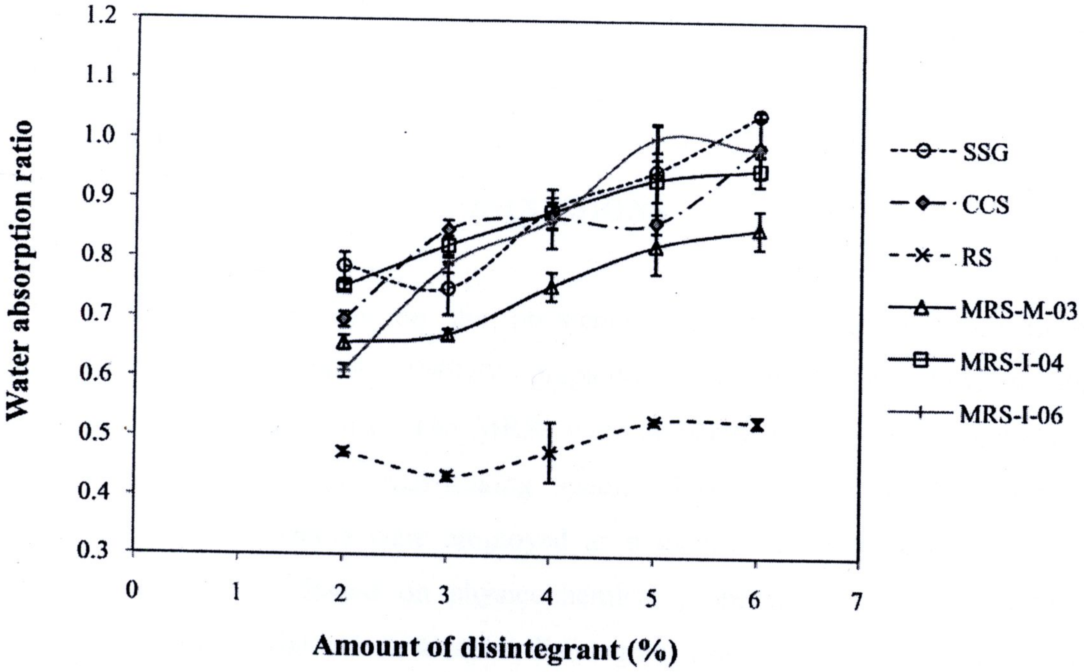


**Figure 3.43** Water absorption ratio (R) of aspirin tablet containing various amounts of disintegrating agents