

Original Research Article

Preparation and Evaluation of Alcohol-Alkaline-Treated Rice Starch as a Tablet Disintegrant

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Abstract

Purpose: To prepare and characterize alcohol-alkaline modified rice starch (MRS) as a disintegrant for tablets.

Methods: The preparation of MRS was carried out using 3 M NaOH and 40 % ethanol solution. Characterization carried out for MRS include morphology, swelling capacity, thermal and pasting properties. Direct-compressed tablets (DCT) containing either propranolol hydrochloride (PPNL) or hydrochlorothiazide (HCTZ) were evaluated for hardness, friability, disintegration time and drug release.

Results: The microstructure of MRS was different in shape and dimension from that of rice starch (RS). The absence of gelatinization endotherm and FT-IR spectral peak for MRS correlated with change in MRS structure and arrangement. MRS showed significantly higher swelling capacity ($p < 0.05$) than RS, and also proved to be a disintegrant in DCT. The disintegration time of the tablets containing MRS was lower in the presence of large particles (3.55 ± 0.56 min); high content of MRS (1.03 ± 0.06 min); low content of lubricant (3.16 ± 0.44 min); water soluble filler (1.55 ± 0.16 min for Super-tab®); and model drug (0.84 ± 0.09 min for HCTZ) ($p < 0.05$).

Conclusion: MRS exhibits improved water solubility and swelling capacity compared with RS, and is thus a good disintegrant for direct-compressed tablet formulations, especially in the presence of water insoluble fillers.

Keywords: Rice starch, Alcohol-alkaline treatment, Disintegrant, Directly-compressed tablet, Insoluble fillers

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INTRODUCTION

Fast-release tablet is one of the widely used dosage forms for oral administration because of convenience and short onset of action, and tablet production by direct compression method is very popular due to the simplicity, low cost and efficiency [1]. Disintegrants are very important substance required for the fast-release of active constituents from tablet dosage forms because

they facilitate the rapid breaking of the tablet into smaller particles [2]. Several compounds have been reported for use as tablet disintegrants including starch, cellulose, povidone and their derivatives [3]. Starch is a natural polymer which is widely employed in pharmaceutical formulations before or after physical and/or chemical modifications with the aim of improving its ability to swell in water, and to confer higher hardness and lower friability to the tablets [4-7].

Alcoholic-alkaline treatment is a simple and inexpensive method of the modification of starch that confers better swelling and higher water solubility at room temperature [6]. This method has been used to modify several starches, such as corn starch, waxy corn starch and sago starch [6,8,9]. Modify waxy maize starches by the method was used as a controlled release matrix [10]. This study focuses on rice starch (RS) that is safe, inexpensive and an important agricultural product of Thailand. RS can be used as pharmaceutical excipient, such as tablet filler in powder form and tablet binder after pregelatinization by heating [10,11]. Unfortunately, RS cannot be used as a disintegrant in tablet because it cannot swell and it is insoluble in water. Thus, the RS modification could possibly improve swelling and water solubility for use in this purpose.

The aim of this study was to investigate the tableting properties of alcoholic-alkaline modified rice starch (MRS) as a disintegrant.

EXPERIMENTAL

Materials

Ethanol (95 %) was purchased from the Liquor Distillery Organization, Thailand. Methanol and citric acid monohydrate were obtained from Prolabo®, EC. Other chemicals and solvents including NaOH (RCI Labscan, Thailand), and hydrochloric acid (Lab-Scan, Ireland) were of analytical grade. Propranolol hydrochloride (PPNL, Changzhou Yabang, China), hydrochlorothiazide (HCTZ, Suzhou Ausun Chemical, China), partially pregelatinized maize starch (Starch 1500®, Rama Production, Thailand), agglomerated lactose (Super-tab®, Meggle, Germany), dibasic calcium phosphate (Di-compresz®, Sudeep Pharma, India), rice starch (Thai Flour Industry, Thailand), sodium starch glycolate (Explotab®, Rama Chem, Thailand), colloidal silicon dioxide (Aerosil® 200, Evonik Industries AG, Germany) and magnesium stearate (Fluka Chemika, Switzerland) were of commercial grade.

Preparation of MRS

MRS was prepared by a method of Chen and Jane [6]. A 200 g of rice starch were suspended in 2000 g of 40 % ethanol solution in a blender mixer for 15 min. Subsequently, the mixture was vigorously stirred with 800 g of 3 M NaOH solution for 90 min. Thereafter, 95 % ethanol (1600 ml) was added to the mixture and stirred

for 15 min at ambient temperature. The solid sediment was allowed to settle and the supernatant was decanted. The precipitate was collected, re-dispersed in 1200 ml of 40 % ethanol solution, and neutralized with 0.5 M citric acid in 800 ml of ethanol. The neutralized starch was collected by filtration and washed using 40 % ethanol and 95 % ethanol, respectively. The filtered MRS obtained was dried in a hot air oven at 50 °C for 24 h. It was milled, sieved (Nos. 100, 140 and 200 meshes), kept in aluminium foil bag, and stored in desiccators at ambient temperature.

Evaluation of MRS

Particle morphology

Shape and size of RS and MRS were observed using scanning electron microscopy (SEM, model JSM-5410LV, JEOL, Japan). Starch sample was mounted onto stub, coated with gold using low vacuum sputter coating, and viewed using the scanning electron microscope.

Differential scanning calorimetry (DSC)

Thermal properties of RS and MRS were analyzed by a differential scanning calorimeter (Model DSC 822, Mettler Toledo, Switzerland). Starch samples (3 mg) were accurately weighed in an aluminum pan, and then 7 µL of purified water was added. Subsequently, the samples were hermetically sealed and allowed to stand for 60 min at room temperature prior to recording the thermogram by heating the sample of starch at a rate of 10 °C/min from 30 - 120 °C, and DSC thermograms were recorded.

Fourier transform infrared (FTIR) spectroscopy

The spectra of RS and MRS were analyzed by FTIR spectrophotometer (Spectrum One, Perkin Elmer, U.S.A). The starch samples were ground with a mortar and pestle together with dried KBr (1:10 w/w), compressed to a disk and analyzed between wave numbers of 4000 and 450 cm⁻¹ at a resolution of 4 cm⁻¹.

Swelling capacity

Starch (0.2 g) was poured into a graduated cylinder 10 ml and recorded the volume (V₀). Ten milliliters of distilled water, 0.1 M HCl or pH 6.8 phosphate buffer were added. The sample was kept at ambient temperature for 24 h and recorded for the final volume (V₁) of the starch gel in the cylinder. Swelling capacity was

calculated as a ratio of V_1/V_0 with three replicates.

Effect of formulation factors on tablet properties

Disintegrant type, particle size and MRS content, lubricant content, filler type and drug type were studied. The tablets were prepared by direct compression method using hydraulic press with 10 mm diameter flat face punch at 100 kgf/cm². The tablet samples were evaluated for their physical properties such as hardness, friability, disintegration time and dissolution time.

To study effect of disintegrant type, MRS, RS and sodium starch glycolate (Explotab®) were used as disintegrants. Each tablet contained 350 mg of Di-Comprez®, 2 % w/w of disintegrant, 1 % w/w of colloidal silicon dioxide and 2 % w/w of magnesium stearate. The effect of particles size of MRS was studied for diameters of < 75, 75 - 106, 106 - 150 µm with the same amount of Di-Comprez®, disintegrant, colloidal silicon dioxide and magnesium stearate.

Three types of fillers, at 350 mg per tablet, were used: Di-Comprez®, Super-tab®, and Starch® 1500. Each formulation contained 2 % w/w of MRS, 1 % w/w of colloidal silicon dioxide and 1% w/w of magnesium stearate.

The effect of MRS content was assessed concentrations of 2, 4, and 8 % w/w. Each tablet contained the same ingredients, viz, 350 mg of Di-Comprez®, 1 % w/w of colloidal silicon dioxide and 1 % w/w of magnesium stearate.

Three concentrations of magnesium stearate at 1, 3 and 5 % w/w were used to study the effect of lubricant concentration on tablet properties. Each tablet contained 350 mg of Di-Comprez®, 2 % w/w MRS, and 1 % w/w colloidal silicon dioxide.

To study the effect of drug types, propranolol hydrochloride (PPNL) 40 mg or hydrochlorothiazide (HCTZ) 50 mg were used. Formulation of each tablet contained drug, Di-Comprez®, 4 % w/w MRS, 1 % w/w colloidal silicon dioxide and 1 % w/w magnesium stearate.

Tablet evaluation

Tablet hardness was measured (n = 10) by a tablet hardness tester (Model VK 200, Vankel®, Benchsarer TM Series, USA). Tablet friability was tested using a friability tester (Model Friabilator, Vankel®, USA) based on USP 34/NF 29 [12]. The disintegration time of tablets was evaluated (n = 6) using a disintegration

apparatus (model QC21, Hanson® Research, USA).

Drug dissolution of PPNL and HCTZ tablets were assessed (n = 6) using a USP type 2 dissolution test apparatus (Hanson Research, Northridge, CA, USA). Drug concentration in dissolution medium was analyzed spectrophotometrically (model UV-1201, Shimadzu, Japan) at 289 and 272 nm for PPNL and HCTZ, respectively.

Statistical analysis

Statistical analysis of the data obtained was carried out using one-way analysis of variance (ANOVA) at 95 % confidence level ($p < 0.05$). Significant differences of mean values were determined by Scheffe's test. The SPSS version 16.0 for windows was used to determine.

RESULTS

Characteristics of RS and MRS

Morphology

RS particles had a polygonal shape with 3 - 10 µm diameter (Figures 1a and 1b), whereas morphology of MRS showed irregular particles with diameter size about 58 – 156 µm (Figures 1c and 1d). MRS did not show starch grains and indented appearance of native RS.

Thermal properties

The DSC pattern of RS showed the temperature of onset, peak and end of gelatinization at 73.22, 75.45 and 79.70 °C, respectively, whereas MRS did not show gelatinization endotherm in the temperature range of 30 – 120 °C (Figure 2), due likely to changes in the internal structure of starch granule during the modification process.

FTIR spectra

RS and MRS showed similar spectra below 800 cm⁻¹ (Figure 3), which is the fingerprint region of starch. This region exhibited the complex vibration mode due to the skeletal mode vibration of glucose pyranose ring [13,14]. MRS showed an obvious change of the peak in the region of 950 - 900 cm⁻¹ when compared with RS, suggesting an alteration of skeletal mode vibration of α-1,4 glycosidic linkage [14]. Moreover, MRS and RS gave similar peaks at approximately 1020, 1079 and 1155 cm⁻¹, corresponding to C-O-H and CH₂-O-CH₂ bonds of glucose structures [13,15,16]. These results

suggested that the backbone glucose units of starch were not changed after modification. The peak of RS at 1370 cm^{-1} originating from CH_2 bending was shifted to higher wavenumber (1399 cm^{-1}). This peak represented a modification of starch chain. The peak at 1648 cm^{-1} of RS was shifted to a lower wave number (1594 cm^{-1}). This was attributed to the water adsorbed in the

amorphous region of starch granules [13,14], leading to a change of crystallinity of RS from crystalline to amorphous form after treatment. In addition, a shift of the peaks of C-H and O-H stretching of RS (2930 and 3393 cm^{-1} , respectively) suggested that change of structure and hydrogen bonding in RS occurred after preparation process [17].

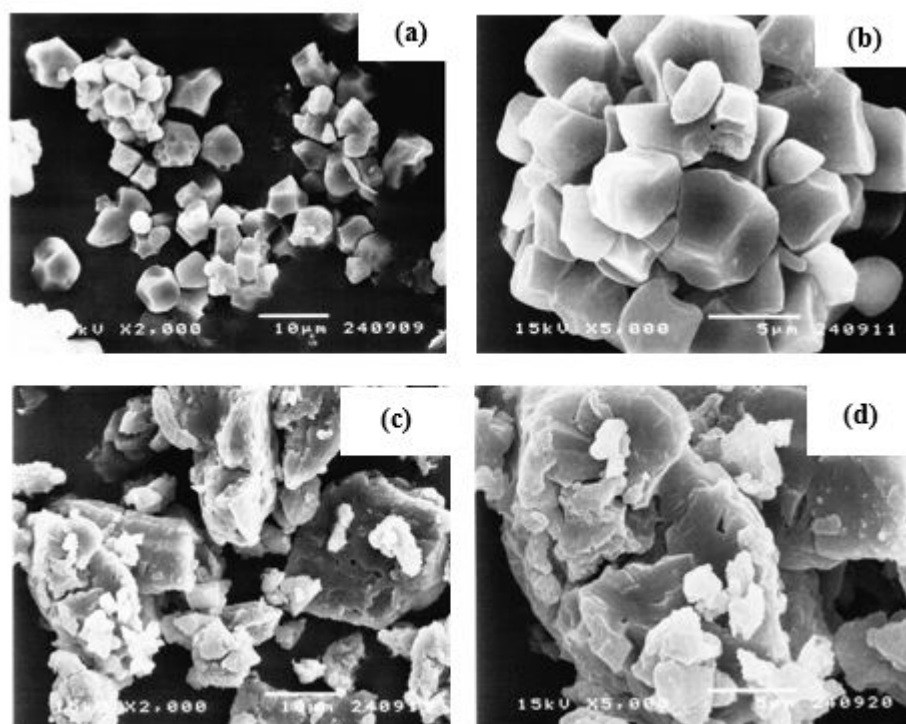


Figure 1: Particle morphology of RS at 2000x magnification (a) 5000x magnification (b); and MRS at 2000x magnification (c), 5000x magnification (d)

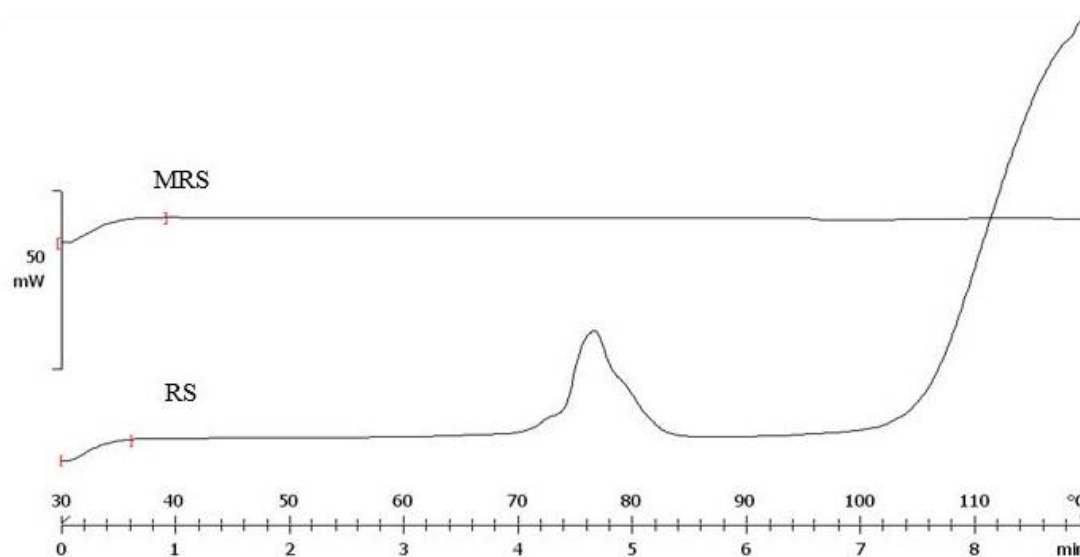


Figure 2: DSC thermograms of RS and MRS

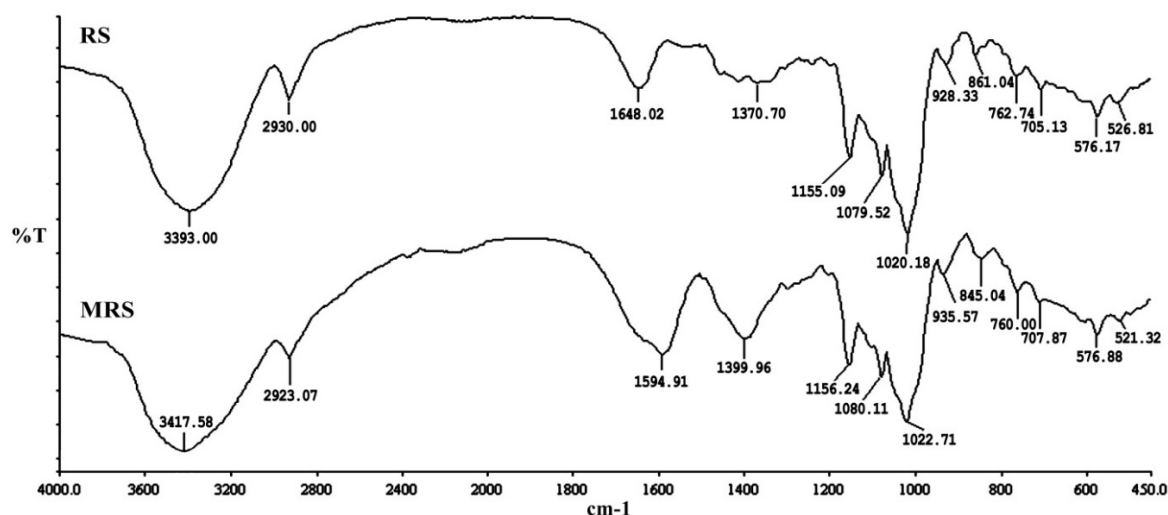


Figure 3: FTIR spectra of RS and MRS

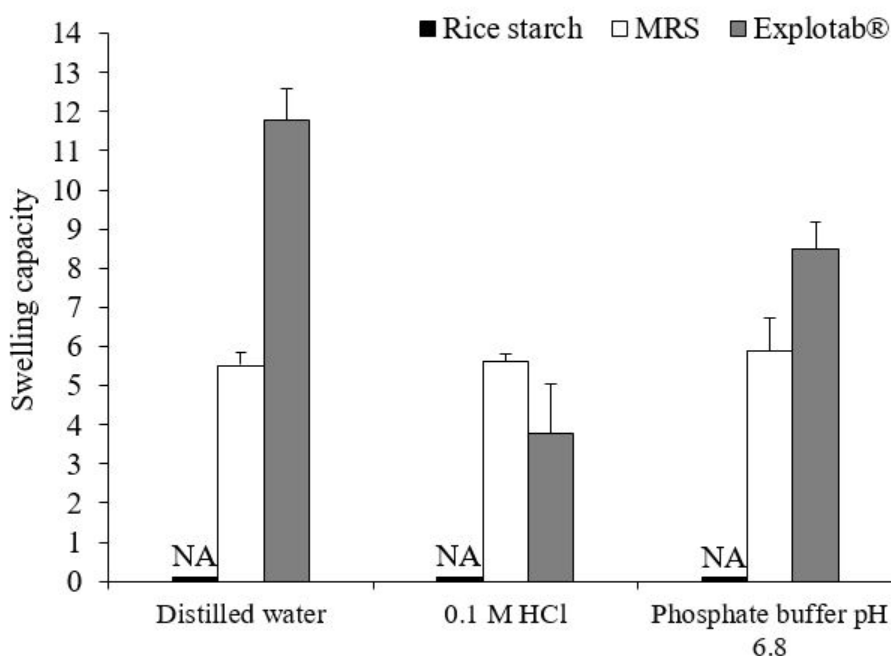


Figure 4: Swelling capacity of RS, MRS and Explotab® in various media

Swelling capacity

RS did not swell in all media used (Figure 4) because the tight packing of amylose and amylopectin chain of RS obstruct water penetration [19]. On the other hand, MRS revealed a pH-independent swelling and the swelling capacity of MRS was statistically higher ($p < 0.05$) than that of RS, whereas Explotab® showed better swelling than MRS in water and phosphate buffer system but less in acid medium. These findings suggested that MRS had strong potential for use as a disintegrant in tablets.

Characteristics of tablets containing MRS

MRS was used as a tablet disintegrant and compared with RS and Explotab® (Table 1). The hardness of tablet was not significantly different ($p > 0.05$). The friability of tablet without disintegrant was lower than those of tablets with disintegrant. The tablets containing MRS gave statistically shorter disintegration time ($p < 0.05$) than those containing RS, but the use of Explotab® resulted in a very short disintegration time.

Table 1: Effect of various ingredients on physical properties of tablets using MRS as a disintegrant

Tablet ingredient	Hardness (kp)	Friability (%)	Disintegration time (min)
Disintegrant			
None	4.16 ± 0.25	2.27	> 180
RS	4.26 ± 0.27	2.36	26.03 ± 4.99
MRS	4.32 ± 0.23	2.61	3.75 ± 0.41
Explotab®	4.02 ± 0.18	2.70	0.84 ± 0.09
MRS particle size			
< 75 µm	4.36 ± 0.17	2.25	4.67 ± 0.68
75-106 µm	4.32 ± 0.23	2.61	3.75 ± 0.41
106-150 µm	4.06 ± 0.19	2.81	3.55 ± 0.56
MRS content (%)			
2	3.90 ± 0.12	2.98	3.16 ± 0.44
4	4.18 ± 0.30	2.29	1.42 ± 0.23
8	4.30 ± 0.23	2.34	1.03 ± 0.06
Filler type			
Di-comprez®	3.90 ± 0.12	2.98	3.16 ± 0.44
Strach 1500®	8.80 ± 0.50	0.40	16.32 ± 2.36
Super-tab®	6.02 ± 0.36	1.92	1.55 ± 0.16
Lubricant content (%)			
1	3.90 ± 0.12	2.98	3.16 ± 0.44
3	4.22 ± 0.16	3.07	8.09 ± 1.65
5	4.82 ± 0.24	2.38	31.68 ± 1.72
Drug type			
PPNL	4.00 ± 0.14	2.36	2.23 ± 0.16
HCTZ	3.82 ± 0.11	2.47	0.82 ± 0.12

Particles size of MRS influenced physical properties of tablets. Increase of MRS particles size caused lower hardness, higher friability and shorter disintegration time (Table 1, rows 7 - 10). Effect of MRS content on tablets was also investigated (Table 1). Increasing MRS content resulted in increased hardness of tablet while disintegration time was decreased.

MRS was used as a disintegrant of tablets prepared using different fillers (Table 1, rows 15 - 18). Starch 1500® and Super-tab® provided higher hardness tablets than Di-comprez®. The friability of Di-comprez® was the highest. Tablet containing Di-comprez® was lower disintegration time than tablet containing Starch 1500® over 5 times. Thus, filler type affected properties of tablets, especially disintegration time. Moreover, magnesium stearate, which used as lubricant, also affected properties of tablets containing MRS. Hardness and disintegration time were significantly increased ($p < 0.05$) with increasing magnesium stearate content (Table 1, row 19-22), whereas friability of tablets tended to decrease with higher magnesium stearate content.

The properties of tablets containing PPNL and HCTZ, high and low water solubility drugs, respectively, were studied (Table 1). Hardness and friability of PPNL and HCTZ tablets were not significantly different ($p > 0.05$). Disintegration time of HCTZ was significantly lower ($p < 0.05$)

than PPNL. Moreover, dissolution profile of both tablets is shown in Figure 5. $T_{50\%}$, i.e. the time to achieve 50 % drug dissolved, of PPNL and HCTZ tablets was 2.54 ± 0.17 and 11.15 ± 1.15 min, respectively, due probably to the difference in drug solubility.

DISCUSSION

The morphology and particles size of RS obtained were similar to that reported by other researchers [18,19]. However, MRS did not appear as granules likely because they were swollen and ruptured during modification process [6,8,20]. The complex structure of RS consists of long chain amylose linked with branch chain amylopectin. The proton of OH group may dissociate leaving negative charges on the starch molecules after treatment with strong base (NaOH). The repulsion between negative charges leads to swelling after water absorption. Then, dissociation of double-helix regions of starches lead to breakdown and change of crystalline structure, and the distortion of starch morphology [8,9]. This structural change following alcoholic-alkaline treatment, causing the disappearance of gelatinization endotherm [8,9,19], was confirmed by FT-IR analysis of position and intensity of infrared band for RS and MRS [21,22]. The intensity of α -1,6 glycosidic linkage of the amylopectin (CH_2 bonding around 1399 cm^{-1} , and OH stretching around 3417 cm^{-1}) of MRS was lower than RS.

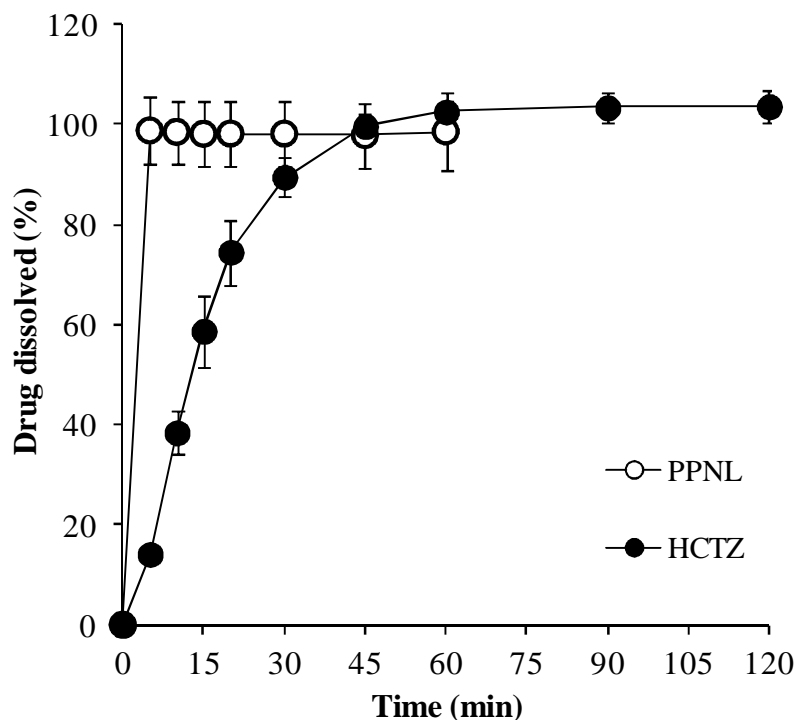


Figure 5: Dissolution profiles of PPNL and HCTZ tablets containing 4 % w/w MRS as a disintegrant

Moreover, the amorphous region of starch where water molecules could be tightly adsorbed (around 1594 cm^{-1}) showed a low absorption, resulting in decreased crystallinity degree of MRS. The molecule of water can interact easier with MRS, resulting in viscosity, swelling and solubility improvement with respect to RS [8]. Consequently, MRS provided better pH-independent swelling capacity than RS.

MRS was used as a tablet disintegrant in comparison with RS and Explotab®, a low substituted carboxy methyl starch (superdisintegrants). MRS showed shorter disintegration time than RS because of higher swelling capacity. Polymer swelling is one of the mechanisms of tablet disintegration; rapid water absorption and swelling of disintegrant caused a break of tablet to smaller particles for enhancing drug dissolution [23]. However, MRS gave longer disintegration time than Explotab®, because of lower swelling capacity of MRS. For particles size of MRS, tablet containing smaller particles of MRS had the highest hardness and the lowest friability because of tightly packing with other ingredients in the tablet. The closed packing of particles caused a retardation of water absorption and swelling of MRS, resulting in longer disintegration time of tablets.

Furthermore, tablet properties were strongly influenced by MRS content. Increase of MRS gave greater hardness and lower friability of the tablets, exhibiting important benefits over native

RS. Moreover, higher disintegrant content allows a rapid uptake of water followed by fast and significantly higher swelling, leading to tablets break up in shorter time. In particular, the highest content (8 %) of MRS showed the best disintegration action in this study.

Tablet properties were dependent upon the filler added. Various types of fillers, such as Dicomprez®, Starch 1500® and Super-Tab®, were used in this study. The tablets containing Super-tab®, lactose anhydrous, had lower disintegration time than those containing Dicomprez®, dibasic calcium phosphate, because water absorption may occur rapidly in tablets prepared using hydrophilic fillers. However, the highest disintegration time was found in the tablets containing Starch1500®. Starch1500® is a partially pregelatinized maize starch that can be partially swollen in water. The swelling of Starch1500® may retard water absorption and then reduce the MRS efficiency for tablet disintegrant. Moreover, the greatest tablet hardness of the tablet containing Starch1500® may also affect the disintegration time.

Lubricant effect is essential in developing a suitable excipient for tablets. In this study, increase in magnesium stearate content provided higher hardness, but lower friability of tablets was obtained. The disintegration time of the tablets significantly increased with increasing magnesium stearate content. These results indicate that the hydrophobicity of magnesium

stearate retarded the absorption of water and polymer swelling which strongly influenced disintegration time, and this is in agreement with the findings of Wang *et al* [24].

MRS was used as a disintegrant in PPNL and HCTZ tablets. The results showed that MRS gave high disintegration efficiency in both tablets, and the disintegration time was in the range of 0.82 - 2.23 min. HCTZ tablets showed faster disintegration time than PPNL tablets. Tablet disintegration normally promotes drug dissolution. However, HCTZ tablets showed slower dissolution rate than PPNL due probably to the lower water solubility of HCTZ.

CONCLUSION

Alcoholic-alkaline treatment changes the structure and properties of RS. The disruption of molecular bonding within the crystalline structure of starch confers enhanced characteristics on MRS, relative to native RS, including higher water solubility and swelling behavior, and faster disintegration. Consequently, MRS has a strong potential for use as an effective disintegrant in directly compressed tablets.

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