PREPARATION OF CROSS-LINKED CARBOXYMETHYL JACKFRUIT STARCH AND EVALUATION AS A TABLET DISINTEGRANT

NISIT KITTIPONGPATANA[1], SUWAKON JANTA[2] AND ORNANONG KITTIPONGPATANA[1*]

[1]*Department of Pharmaceutical Sciences, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand*

[2]*Department of Science, Faculty of Science and Technology, Chiang Mai Rajabhat University, Chiang Mai, Thailand*

ABSTRACT

The main purposes of this study are to prepare cross-linked carboxymethyl jackfruit starch (CL-CMJF) and to evaluate its pharmaceutical property as a tablet disintegrant. CL-CMJF was prepared by a dual carboxymethyl-crosslinking reaction in a flask containing jackfruit seed starch (JFS), chloroacetic acid (CAA), sodium hydroxide (NaOH) and sodium trimetaphosphate (STMP). The reaction was carried out using methanol as a solvent for 60 min at 70°C and at JFS:CAA:NaOH:STMP ratio of 1.0:0.29:0.28:0.07. The obtained CL-CMJF, with degree of substitution and degree of crosslinking calculated to be 0.34 and 0.06, respectively, was insoluble but swellable in water. Rheological study revealed a decreased in solution viscosity compared to the non-crosslinked CMJF. The water uptake of CL-CMJF was 23 times higher than that of native starch and was comparable to that of a commercial superdisintegrant, sodium starch glycolate (SSG). The swelling ability of CL-CMRS was similar to that of crosscarmellose sodium (CCS), another commercial superdisintegrant. Disintegration test of aspirin tablets containing 2%w/w of JFS, CL-CMJF, SSG and CCS showed disintegration times in the order of SSG < CCS ~ CL-CMJF <<< JFS. The results suggested that CL-CMJF could be developed as a tablet disintegrant.

Keywords: *Artocarpus heterophyllus*, carboxymethyl starch, cross-link, jackfruit seed, tablet disintegrant

INTRODUCTION

Seeds of jackfruit (*Artocarpus heterophyllus* Lam., Moraceae), widely regarded as biowaste material, contain approximately 20% starch on dry weight basis that can potentially be extracted and purified for industrial uses. Research studies on the extraction and physicochemical properties of jackfruit starch (JFS) revealed several unique characteristics, including granule shape, thermal and mechanical properties, and acid resistance, compared to common starches (Bobbio *et al*., 1978; Tulyathan *et al*., 2002; Mukprasirt and Sajjaanatakul, 2004; Tongdang 2008). Until recently, utilization of JFS has been limited to the food products and a few pharmaceutical applications (Kavitha *et al*., 1992; Khunkitti *et al*., 2006; Rengsutthi and Charoenrein, 2010).

Starch and modified starches have been commonly employed as excipient in pharmaceutical industry, particularly in the manufacturing of tablets. The use of non-modified or "native" starch, however, is mostly confined to as diluent or filler, due to limitation in several physicochemical properties. The modification of native starch, either by physical or chemical methods, normally resulted in modified starches with improved functionality. Examples of common modifications include pregelatinization, acid-treatment, cross-linking, hydroxypropylation, and carboxymethylation. These reactions can be carried out individually, sequentially or simultaneously. The combination of carboxymethyltion and cross-linking reactions has been reported on several native starches, using a broad range of cross-linking agents (Kaur *et al*., 2006; Kittipongpatana *et al*., 2010). Carboxymethyl starch (CMS) is a chemically-modified starch which has found many uses in the food and pharmaceutical industries (Kittipongpatana *et al*., 2006; Brouillet *et al*., 2008). Carboxymethylation increases the hydrophilicity and enhances water uptake and solubility of starch, while cross-linking reaction decreases water solubility due to the bridging of starch chains. The dual reaction leads to either an increase in solution viscosity due to restricted chain movement or a decrease in viscosity with improved swelling, depending on the concentration of cross-linking agent used (Kittipongpatana *et al*., 2010). Although JFS has not been researched as an excipient in solid dosage form, starch from a related source (*Artocarpus communis*, known as Breadfruit), with some similar physicochemical properties, was reported to possess tablet disintegrating property (Adebayo *et al*., 2008). Therefore, modification of JFS by carboxymethylation with suitable level of cross-linking could yield a modified starch with good disintegrating property. This study reports the preparation of carboxymethyl jackfruit starch cross-linked with sodium trimetaphosphate (CL-CMJF) and the evaluation of its pharmaceutical property as a tablet disintegrant.

MATERIALS AND METHODS

Materials

Native jackfruit starch (JFS) was extracted from seeds of jackfruit (*Artocarpus heterophyllus* Lam.) variety Thong Prasert. Seeds were processed by lye-peel method (Tulyathan *et al*., 2002) to obtain flour, which was then

**Corresponding author:* e-mail: ornanong@pharmacy.cmu.ac.th

extracted using a method modified from that described for isolation of jackfruit starch (Bobbio *et al*., 1978). In brief, 600 mL of 0.05 *M* NaOH was added into a 200-g portion of jackfruit flour and stirred for 5 h at room temperature. The suspension was filtered through wire mesh 75 μm. The slurry was then allowed to settle overnight at <10°C and the supernatant was discarded. The sediment was washed with 600 mL water three times. Then 600 mL water was added and the pH was adjusted to 7.0 with 1 *M* HCl. The mixture was allowed to settle and the supernatant as well as the dark layer on top was discarded. Finally, the extracted starch was washed six times, each with 600 mL of water, and the mixture was allowed to settle before the supernatant discarded. Following an air-dry and a subsequent oven-dry at 40ºC for 12 hours, the native starch powders were ground to pass sieve no.60 before use. All chemicals used in the preparation of cross-linked carboxymethyl jackfruit starch (CL-CMJF) were of analytical reagent grade or equivalent. Crosscarmellose sodium (CCS) and sodium starch glycolate (SSG), the standard disintegrants, were gifts from Biolab Co.Ltd. (Bangkok, Thailand)

Preparation of CL-CMJF

Chloroacetic acid (CAA, 40 g) was dissolved in 254 g MeOH. Then, while stirring, 138 g JFS powder was added into the solution followed by 78.5 g of 50% w/w NaOH solution. Sodium trimetaphosphate (STMP) was then added into the reaction. The mixture was heated up to 70ºC and steadily maintained for 60 minutes with continuous stirring. At the end, the reaction was ceased by neutralization with glacial acetic acid. The liquid supernatant was decanted and the powder product was washed several times with 80% methanol until the filtrate gave no precipitate when tested with silver nitrate solution and a final wash with 100% methanol. The JFS: CAA: NaOH: STMP ratio were 1.0: 0.29: 0.28: 0.07. Degree of substitution (DS), degree of cross-linking (DCx) was determined as described in (Kittipongpatana *et al*., 2010). Reaction efficiency (RE; %) was calculated as described by Wang *et al*. (2010).

Physicochemical Evaluations

Moisture Content

The sample (5 g) was placed on the pan of a Kett F-IA moisture content balance. The exact weights of sample before and after being heated to a constant weight were recorded. The moisture content was then calculated.

Hausner ratio and Carr's indices

The bulk and tapped densities of JFS and CL-CMJF were determined according to standard USP method (USP/NF, 2010). Hausner ratio was calculated as the ratio of the bulk density to the tapped density. Carr's index was the percentage ratio of the difference of both densities to the tapped density (Well and Aulton, 2001). The Carr's index was used to designate the flowability of the sample.

SEM analysis

Scanning Electron Microscopy (SEM) experiments to analyze the granule surface, shape and size were conducted using a Phillip XL 30 ESEM (FEI company, Hillsboro, Oregon, USA) equipped with a large field detector. The acceleration voltage was 10-20 kV under low vacuum mode (0.7-0.8 torr).

X-ray diffraction

X-ray diffraction patterns were recorded in the reflection mode on a Siemens D-500 X-ray diffractometer. Diffractograms were registered at Bragg angle (2θ) range of 5-40° at a scan rate of 2.5° per minute and step size of 0.02°.

Water solubility and swelling power

The solubility in water and swelling power of samples were determined by adding 0.1 g of sample into each of a pre-weighed centrifuge tubes containing 10 ml water (1% w/v), mixed thoroughly for 1 min using a Vortex mixer. The tubes were allowed to stand for 10 min, then centrifuged at 3000 rpm for 15 min. The supernatant was transferred into a pre-weighed crucible and dried to a constant weight at 120°C. The weights of the dried residue and of the sedimented paste were used to calculate the solubility percentage and the swelling power, respectively (Nwokocha and Williams, 2009).

Viscosity

Apparent viscosity was measured using a Brookfield R/S-CPS rheometer (Bob-and-Cup format). The measuring system was CC48 DIN. The mode used was CSR (controlled shear rate). The measured parameters consisted of three steps: (1) an increase of the shear rate from 0 to 100 s^{-1} in 1 min, (2) held at 100 s^{-1} for 1 min and (3) a decrease of the shear rate from 100 to 0 s^{-1} in 1 minute. All measurements were performed in triplicate, at a controlled temperature of 25±1ºC. The data were analyzed with a Brookfield Rheo 2000 software. The apparent viscosity for all samples in this study was measured at a shear rate of 100 s^{-1}. Viscosity was expressed in Pa.s.

Water uptake

Water uptake of CL-CMJF was carried out using an apparatus described by Nogami *et al*. (1969). The sample (500 mg) was loaded into a holder which was then placed onto the apparatus. The volume of water taken by the sample was recorded at 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 10.00, 15.00, 20.00, 25.00, 30.00, 40.00, 50.00 and 60.00 min. Each sample was tested in triplicate.

Pharmaceutical property as tablet disintegrant

Aspirin tablets, containing 325 mg aspirin, 2%w/w disintegrant, 3% w/w purified talcum and 0.5%w/w magnesium stearate, were prepared by direct compression

method at compression force of 2 tons. The disintegrants were one of the following: JFS, CL-CMJF, SSG or CCS. Disintegration was preliminarily tested by dropping the tablet into a beaker of water, then observed the disintegration behavior at time 0, 1 and 3 min. Determination of disintegration time was carried out according to standard method described in the United States Pharmacopeia (USP/NF, 2010).

STATISTICAL ANALYSIS

All tests were performed at least in triplicate. The statistical significant tests were performed using analysis of variance (ANOVA) at 95% confidence level ($p<0.05$). Significant differences among mean values were determined by Duncan's multiple range test.

RESULTS

CL-CMJF was obtained as fine, off-white, poor-flowing powder, similar to the two standard disintegrants used. Degree of substitution (DS) was 0.34. The reaction efficiency was 61.8%. The phosphate content was 0.59±0.01%, which was equivalent to a degree of crosslinking (DCx) of 0.063 according to the calculation suggested by Deetae *et al*. (2008). Physical properties of CL-CMJF, in comparison with JFS are presented in table 1.

Table 1: Physical properties of jackfruit starch (JFS) and cross-linked carboxymethyl jackfruit starch (CL-CMJF)

Physical Properties	JFS	CL-CMJF
Moisture Content (%)	6.21	8.27
Bulk Density (g/ml)	0.54	0.56
Tapped Density (g/ml)	0.75	0.75
Flow Properties	Poor	Poor
Carr's Index	27.08	25.00
Hausner Ratio	1.37	1.33

SEM image of CL-CMJF (fig. 1a) showed slight changes in granule surface compared to that of JFS (fig. 1b), with detection of small fragments. XRD result (fig. 2) showed only a slight decrease in crystallinity of CL-CMJF compared to that of JFS.

CL-CMJF was slightly soluble in water. Its solubility was significantly greater (>7x) than that of JFS (table 2). However, the viscosity of 1%w/v solution CL-CMJF was much lower (>5x) than that of the water-soluble CMJF. On the other hand, CL-CMJF exhibited significant water swelling. The rate of water uptake at the beginning was similar to that CCS but remained significantly lower than that of SSG (fig. 3).

Disintegration test of aspirin tablets containing 2%w/w of JFS, CL-CMJF, SSG or CCS as disintegrant are shown in Figure 4A-D. After 1 min of water exposure, tablets containing 2% CL-CMRS, SSG or CCS started to swell and exhibited disintegration, which continued to increase and reached a maximum point after 3 min. In contrast, tablets containing 2% JFS showed no swelling after 1 min and only slight swelling after 3 min. Disintegration times of tablets containing different disintegrant were in the order of SSG < CCS < CL-CMJF <<< JFS <<< control (no disintegrant) (table 3).

DISCUSSION

The preparation procedures for CL-CMJF utilized non-toxic, aqueous-alcoholic solvent and generated no waste other than NaCl salt from the neutralization step, which was eliminated in the washing step. The cross-linking reagent used (STMP) was also classified as GRAS (generally recognized as safe) substance. Higher moisture content suggested that CL-CMJF was more hygroscopic compared to JFS, which could be a result of the improved ability to take up water. The flowability was not different from that of JFS, according to Carr's index and Hausner ratio.

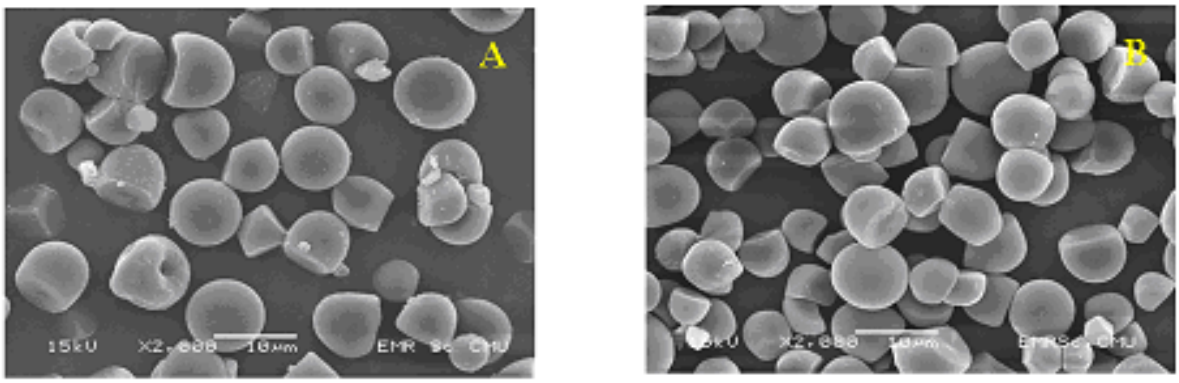

Fig. 1: Scanning electron microscopic (SEM) images of cross-linked carboxymethyl jackfruit starch (CL-CMJF) (A) and jackfruit starch (JFS) (B).

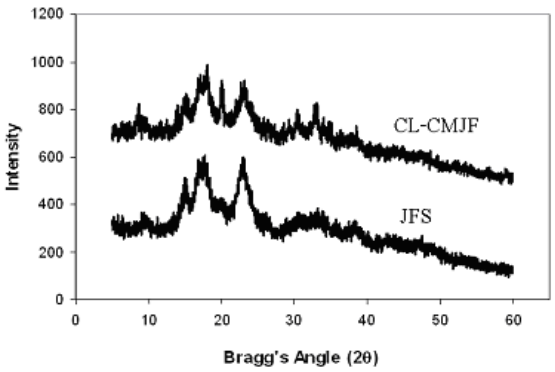

Fig. 2: X-ray diffraction (XRD) images of jackfruit starch (JFS) and cross-linked carboxymethyl jackfruit starch (CL-CMJF)

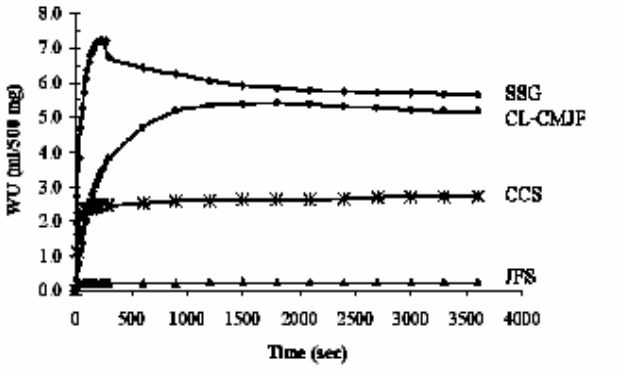

Fig. 3: Water uptake of jackfruit starch (JFS) and cross-linked carboxymethyl jackfruit starch (CL-CMJF) compared to standard superdisintegrants, sodium starch glycolate (SSG) and crosscarmellose sodium (CCS)

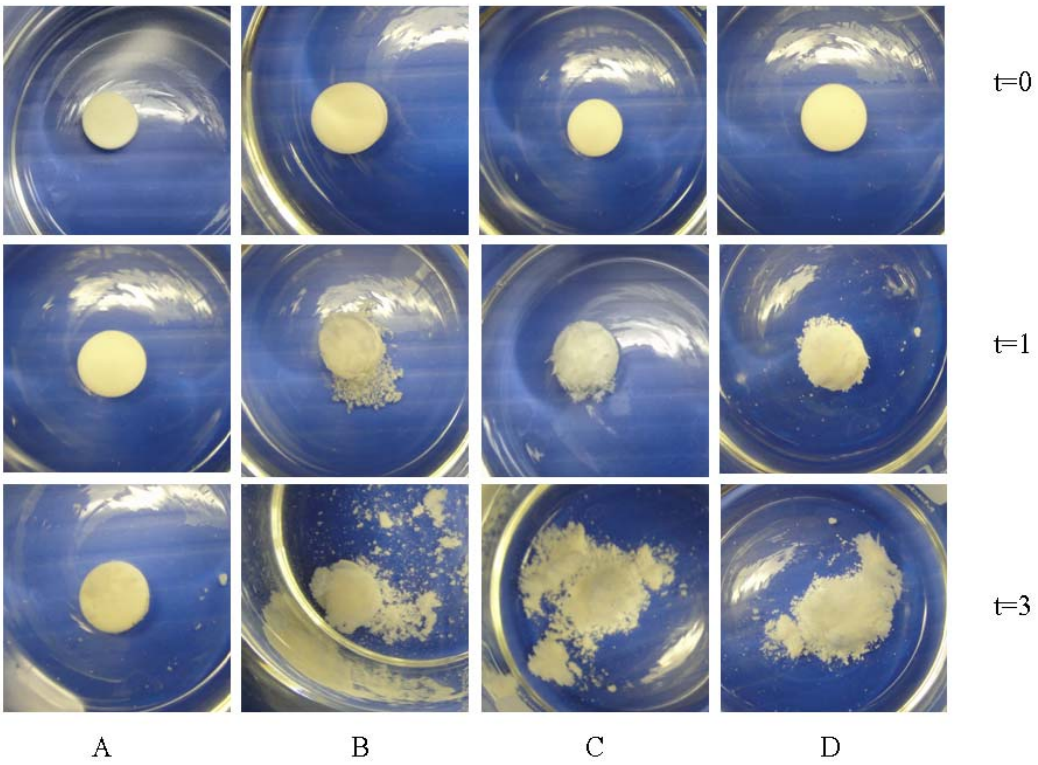

Fig. 4: Disintegration of tablets containing jackfruit starch (A), cross-linked carboxymethyl jackfruit starch (B), sodium starch glycolate (C) and crosscarmellose sodium (D) as disintegrant at 2%w/w. Pictures taken at t= 0, 1 and 3 min.

Small fragments detected in the SEM image of CL-CMJF were due to cross-linking reaction as suggested by Wang *et al*. (2010). This is similar to the results reported for cross-linked rice starch (Kittipongpatana *et al*., 2010). Cross-linking was suggested to take place mainly in the non-crystalline region, thus had very little effect on the crystallinity of the modified starch (Koo *et al*., 2010).

The solubility of CMJF was similar to that of CCS and SSG. The swelling power of CL-CMJF was between those of CCS and SSG, which was >25 times higher than that of JFS. The final water uptake volume (ml/g dry starch) of CL-CMJF was comparable to that of SSG and was 2 and 23 times higher than that of CCS and JFS, respectively. Water uptake and swelling power are main

Table 2b: Solubility, swelling power, final water uptake volume and viscosity (1% w/w solution) of jackfruit starch (JFS), carboxymethyl jackfruit starch (CMJF) and cross-linked carboxymethyl jackfruit starch (CL-CMJF) compared to standard superdisintegrants

Sample	Water Solubility (%)	Swelling Power (g/g starch)	Final Water Uptake (ml/500 mg)	Viscosity (mPa.s ± SD, n = 3)
JFS	0.40±0.05	1.13±0.04	0.23±0.06	ND
CMJF	ND	ND	1.22±0.24	174.3±1.4
CL-CMJF	3.05±0.27	29.11±4.01	5.17±0.51	31.0±0.6
SSG	3.77±0.23	51.26±2.56	5.83±0.87	8.5±1.7
CCS	3.28±0.45	18.75±3.22	2.66±0.23	27.5±1.3

ND – not determined

parameters that indicate the potential of an excipient as a tablet disintegrant. Good disintegrants take up water and swell rapidly, creating "pushing" force inside the tablet that eventually overcome the "binding" force between particles, resulting in the breakage of a tablet (Lieberman *et al*., 1989).

Tablets containing JFS disintegrated faster than those containing no disintegrant, suggesting that JFS also possessed disintegrating property, although not very effective. Control tablets disintegrated mainly by erosion. CL-CMJF exhibited only slightly longer disintegration time compared to SSG or CCS and could be further developed as a tablet disintegrant. CMJF retarded disintegration, similar to previous reports on CMRS (Kittipongpatana *et al*., 2007) and could be a candidate for a controlled release matrix (Brouillet *et al*., 2008).

Table 3: Disintegration time (DT) of aspirin tablets containing 2%w/w jackfruit starch (JFS), carboxymethyl jackfruit starch (CMJF) or cross-linked carboxymethyl jackfruit starch (CL-CMJF) as disintegrant compared to standard superdisintegrants

Disintegrant	DT (min)
none	8.42
JFS	4.44
CMJF	11.49
CL-CMJF	1.02
SSG	0.42
CCS	0.56

CONCLUSIONS

Cross-linked carboxymethyl jackfruit starch (CL-CMJF) was successfully prepared by a dual, simultaneous reaction using non-toxic chemicals and solvents. Physicochemical properties and a pharmaceutical property as tablet disintegrant were evaluated. CL-CMJF was insoluble in water but exhibited swelling ability in the same magnitude of crosscarmellose sodium, a standard disintegrant. Rheological evaluation showed a decrease in solution viscosity compared to the non-crosslinked CMJF. The water uptake profile of CL-CMJF was similar to that of CCS, while the uptake volume was up to 23 times higher than that of JFS. Disintegration test in aspirin tablets supported that CL-CMJF could be developed as a tablet disintegrant.

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