Carbohydrate Polymers 88 (2012) 1195–1200

Contents lists available at SciVerse ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Facile synthesis of starch-maleate monoesters from native sago starch

Soon Hiang Tay, Suh Cem Pang*, Suk Fun Chin

Department of Chemistry, Faculty of Resource Science and Technology, University Malaysia Sarawak, 94300 Kota Samarahan, Sarawak, Malaysia

ARTICLE INFO

Article history:
Received 5 September 2011
Received in revised form 23 January 2012
Accepted 25 January 2012
Available online 2 February 2012

Keywords:
Sago starch
Starch-maleate monoester
Cross-linked particles
Green synthesis

ABSTRACT

This paper documented a facile and green approach for synthesizing water soluble cross-linked starch-maleate monoester gel particles from native sago starch (*Metroxylon sagu*). Starch-maleate (SM) monoester gel was initially synthesized by reacting sago starch with maleic anhydride in an aqueous medium, and followed by precipitating in absolute ethanol. The transformation of starch-maleate gel into cross-linked gel particles of mean diameter 445 ± 115 nm occurred upon UV irradiation in the presence of cerium(IV) ammonium nitrate. The substitution of maleic anhydride onto starch chains was confirmed by FTIR spectroscopy, and the degree of substitution (DS) as determined by the back-titration method was within the range of 0.03–0.21. The water absorbency and hydrophilicity of SM samples of $DS < 0.03$ was substantially lower than SM samples of $DS > 0.08$. Being non-toxic, biocompatible and cheap, the potential utility of starch-maleate gel particles as drug delivery carriers in biomedical applications is therefore envisaged.

1. Introduction

In recent decade, numerous biomedical applications based on the utilization of natural polymers such as proteins (e.g. collagen, gelatin and albumin) and polysaccharides (e.g. starch, dextran, cellulose and chitosan) had been reported (Elfstrand et al., 2007; Liu, Chen, Li, Hu, & Cai, 2004; Shanbhag, Barclay, Koziara, & Shivanand, 2007; Tiyaboonchai, 2003). Recently, starch derivatives have been studied for potential applications in the controlled release of therapeutic agents (Alias, Silva, Goni, & Gurruchaga, 2008; Bravo-Osuna, Ferrero, & Jiménez-Castellanos, 2008; Chen, Li, Li, & Guo, 2007). Starch derivatives are inexpensive biomaterials which exhibit bioavailability and biocompatibility properties in biological fluid. Due to the presence of abundant and freely available hydroxyl groups on the starch chains, starch can be easily modified and tailored for various desired applications (Sun & Sun, 2002). The hydroxyl groups of starch chains can be etherified through the formation of free radicals, or esterified with carboxylic acid, acyl chloride as well as acid anhydride (Chi et al., 2008; Fang, Fowler, Sayers, & Williams, 2004). Various sources of starch have been utilized as the precursors for the preparation of a wide range of starch derivatives suitable for pharmaceutical applications (Elfstrand et al., 2007). Starch derivatives of high amylose maize were investigated as effective colon-targeted drug delivery carrier (Alias et al., 2008) and gastrointestinal tract drug delivery carrier (Desai, 2007). High amylose Hylon VII starch was investigated as starch excipients for transmucosal delivery (Mulhbacher, Ispas-Szabo, Ouellet, Alex, & Mateescu, 2006). Maize starch derivative was evaluated as a potential drug delivery carrier for colon-targeting biomacromolecule drugs (Chen et al., 2007). However, little or no study has been conducted on the utilization of sago starch derivatives for biomedical applications.

In the modification and derivatization of starch, an appropriate solvent medium is essential for the effective solubilization of starch granules, and subsequent dissolution of their amylose and amylopectin components. Upon dissolution, hydroxyl groups on the polysaccharide chains become accessible to electrophillic substitution during the esterification reaction. The solubilization of starch during esterification was commonly being conducted in aprotic solvents such as LiCl/dimethylacetamide and dimethylsulfoxide (DMSO) (Biswas, Shogren, Kim, & Willett, 2006; Fang et al., 2004). These solvent systems were harmful and difficult to be removed from the end products, and hence rendered them unsuitable for biomedical applications. Nevertheless, the successful starch esterification in aqueous media with a moderate degree of substitution had been reported (Xu, Miladinov, & Hanna, 2004). It is noteworthy that sodium hydroxide is commonly being used as a catalyst in aqueous starch esterification instead of using toxic reagents such as *N*,*N*-dimethylaminopyridine, methane sulphonic acid (Biswas et al., 2006; Chi et al., 2008; Fang et al., 2004; Wang & Wang, 2002). Enhanced starch solubility in alkaline medium had resulted in high accessibility of reagents and hence uniform substitution.

Although the preparation of starch esters with substituted hydrophobic end groups such as acetylated starch have been frequently reported (Gunaratne & Corke, 2007; Roesser, McCarthy, Gross, & Kaplan, 1996), little attention has been focused on starch

---

* Corresponding author. Tel.: +60 82 583017; fax: +60 82 583160.
E-mail addresses: scpang@frst.unimas.my, suhcem@gmail.com (S.C. Pang).

0144-8617/$ – see front matter
doi:10.1016/j.carbpol.2012.01.079

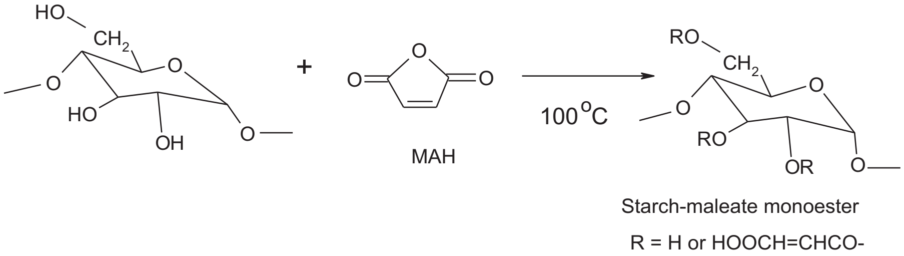


Fig. 1. Schematic representation of the reaction between sago starch and maleic anhydride.

monoesters derived from dicarboxylic acids such as maleic acid, fumaric acid and succinic acid (Yoshimura, Yoshimura, Seki, & Fujiok, 2006). Biswas et al. (2006) prepared starch maleate half-esters of degree of substitution (DS) up to 0.25 using microwave assisted heating with DMSO and pyridine being used as the solvent and catalyst, respectively. Maleic acid and fumaric acid form unsaturated polyesters with starch, and these resulting macromolecules are stabilized by the formation of cross-linked networks via photocuring of the unsaturated double bonds of dicarboxylic acids (Mahmoudi, Simchi, Imani, & Hafeli, 2009).

In this study, we have successfully synthesized starch-maleate (SM) monoester gels of DS up to 0.21 in an aqueous medium by a facile and green synthesis approach using non-toxic precipitating media (ethanol, propan-2-ol, or butan-1-ol). Starch-maleate monoester gels were transformed into discrete spherical gel particles upon UV irradiation of SM solution in the presence of cerium(IV) ammonium nitrate, and subsequently precipitated in absolute ethanol under controlled conditions. The physico-chemical characteristics and properties such as surface morphology, particle size, degree of substitution, and moisture absorbency of both starch-maleate monoester gels and cross-linked starch-maleate monoester gel particles (CSM) were investigated.

2. Experimental

2.1. Materials

Native sago starch powder was obtained from a local grocery store (Commercial Food grade, 27% amylose). Sodium hydroxide (AR grade, Cat No. 7708-12) was supplied by Mallinckrodt. Cerium(IV) ammonium nitrate (Cat. No. 1.02276.0100), maleic anhydride (Cat. No. 8.00408.1000), butan-1-ol (Cat. No. 1.01990.2500) and propan-2-ol (Cat. No. 1.09634.2511) were purchased from Merck; Absolute ethanol (GPR grade) was purchased from Hamburg. All chemicals were used without further purification. Ultrapure water (18.2 MΩ) was used in all syntheses.

2.2. Synthesis of starch-maleate monoester gels

Starch-maleate monoester gels were prepared by esterification of starch in an aqueous medium (Fig. 1). Typically, about 8.0 g of sago starch (0.05 mol anhydroglucose unit or AGU) was added into different volumes of ultrapure water (10 mL, 50 mL or 100 mL) in a conical flask. The dispersion mixture was stirred while the required amount of 2.0 M NaOH solution (50 mL, 25 mL or 12.5 mL) was added. The dispersed starch solution was slowly gelatinized to form a dark brown solution. 7.4 g of maleic anhydride (MA) (1.5 mol MA to 1.0 mol of AGU) was then added to the gel which gradually turned into a less viscous and pale yellowish solution. The resulting mixture was stirred continuously at 100 °C for 4 h. Upon completion of reaction, the mixture was cooled to room temperature, and the soluble SM product was isolated by precipitation with 50 mL of various precipitating media (ethanol, propan-2-ol or butan-1-ol) at room temperature. The pinkish white precipitate was collected by vacuum filtration, rinsed three times with pure precipitating media to remove excess maleic anhydride, and then dried overnight at 60 °C in a conventional oven. These SM samples (0.15 g) were further purified by dissolving them in ultrapure water (15 mL) and re-precipitated by adding SM solutions dropwise into absolute ethanol (30 mL) under constant stirring. All SM precipitates were then dried overnight at 60 °C in a conventional oven.

2.3. Preparation of cross-linked starch-maleate monoester gel particles (CSM)

About 1.30 g of SM with DS = 0.21 (0.05 mol anhydroglucose-maleate unit) as prepared previously was dissolved in 10 mL of ultrapure water in a glass vial. 5 mL of 1.0 M cerium(IV) ammonium nitrate solution was then added into the SM solution. The reaction mixture was purged with purified nitrogen gas to remove dissolved oxygen. In this study, a UV lamp of short wavelength (254 nm) and a power of 6 W was positioned at a distance of about 1 cm from the sample in a tightly sealed vial. The reaction mixture was continuously stirred while being irradiated with UV light at ambient temperature for 8 h. The resulting reaction mixture was added dropwise into 30 mL of absolute ethanol under constant stirring. The resulting white pinkish precipitate of CSM was collected by vacuum filtration and dried overnight at 60 °C in a conventional oven.

2.4. Characterization of SM and CSM

Fourier transformed infrared (FTIR) spectra of native sago starch, SM and CSM samples were obtained from KBr/sample pellets, using a PerkinElmer System Spectrophotometer within the wavenumber range of 4000–400 cm^{-1}.

The morphology of SM and CSM samples were studied by SEM (JEOL JSM-6390LA) with an accelerating voltage of 10–15 kV. The CSM samples were pre-coated with a thin layer of platinum to reduce the charging effect during SEM imaging. SEM micrographs were generated at three randomly selected spots of samples from which the mean particle size and size distribution of dispersed CSM samples were determined. The mean particle diameter (D_n) of CSM was determined by randomly measuring at least 50 discrete and spherical CSM particles. according to Eq. (1) (Arnal, Matos, Morales, Santana, & Müller, 1998):

$$D_n = \frac{\sum n_i d_i}{n_i} \tag{1}$$

where n_i is the number of particles of diameter d_i.

The degree of substitution (DS) of SM was determined according to the method reported by Xu et al. (2004) with some modifications. Typically, a known weight of the SM sample was dissolved in 10 mL of 0.1 M NaOH with stirring at ambient temperature for

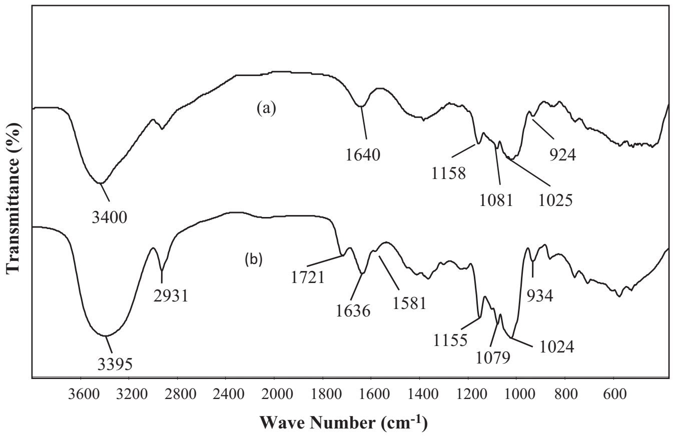


Fig. 2. FTIR spectra of (a) native sago starch, and (b) starch-maleate monoester (DS = 0.21) which was precipitated in absolute ethanol.

30 min. The excess NaOH was back-titrated with standard 0.2 M HCl using phenolphthalein as the indicator. The titration was repeated twice, and the average volume of HCl was corrected against the control sample as blank. The DS of SM sample was calculated using Eq. (2):

$$\mathrm{DS} = \frac{162 \times n_{\mathrm{COOH}}}{m - 99 \times n_{\mathrm{COOH}}} \tag{2}$$

where 162 g/mol is the molar mass of an AGU, 99 g/mol is the net increase in the mass of an AGU for each maleate molecule substituted, m is the weight of sample analyzed, and n_{COOH} is the amount of COOH calculated from the average titrated volume of standard HCl according to Eq. (3):

$$n_{\mathrm{COOH}} = V_{\mathrm{NaOH}} \times C_{\mathrm{NaOH}} - V_{\mathrm{HCl}} \times C_{\mathrm{HCl}} \tag{3}$$

The moisture absorbency of the SM sample at room temperature was evaluated after it has been equilibrated in a relative humidity of 100% for 6 days. A known amount of the sample was placed inside a plastic container and maintained at a constant relative humidity (RH) of 100%. The moisture absorbance of the SM sample was calculated according to Eq. (4):

$$\text{Moisture absorbency}\,(\%) = \frac{W_{\mathrm{a}} - W_{\mathrm{b}}}{W_{\mathrm{b}}} \times 100 \tag{4}$$

where W_{b} and W_{a} are the weight of the samples before and after equilibration, respectively.

3. Results and discussion

3.1. Evidences of maleate substitution on starch molecules

Fig. 2 shows the FTIR spectra of native sago starch and SM samples. The SM sample showed an absorption band at 1721 cm^{-1} which could be attributed to the carbonyl group of maleate moiety in the substituted starch (Pang, Chin, Tay, & Tchong, 2011; Raquez et al., 2008). The absorption peak at 1581 cm^{-1} could be attributed to the C=C bond of the maleate moiety (Thakur, Chauhan, & Ahn, 2009), and non-symmetric deformation of the carboxylate ($-\mathrm{COO}^-$) group (Rivero, Balsamo, & Müller, 2009). The absence of absorption peaks at 1787 and 1857 cm^{-1} which corresponded to ring anhydride carbonyl group showed that no maleic anhydride remained in the sample (Wu, 2003). In the fingerprint region, several peaks were observed at 1155, 1079, 1024 and 934 cm^{-1}, which could be attributed to C–O bond stretching of sago starch (Fang et al., 2004). The peaks at 1079 and 1024 cm^{-1} were characteristic of the anhydroglucose ring O–C stretching, indicating that there was no ring opening of the anhydroglucose unit during the substitution reaction (Sun & Sun, 2002). In other words, the structural integrity of the anhydroglucose unit was retained in the substituted sago starch. A characteristic peak occurred at 1636 cm^{-1}, which was presumably a feature of tightly bound water present (Kacurakova & Wilson, 2001), and overlapped with the C=C stretching of maleate moiety on the starch chains (Liou & Wang, 1996). An extremely broad band due to hydrogen bonded hydroxyl groups (OH) appeared at 3395 cm^{-1} which was attributed to the complex vibrational stretches associated with free, inter and intra-molecular bound hydroxyl groups of the starch chains (Pal et al., 2008). The absorption band at 2931 cm^{-1} was characteristic of the C–H stretching (Elvira, Mano, San Roman, & Reis, 2002). These results indicated the feasibility of substituting the carboxylic group of maleic anhydride onto the starch chains to form SM monester.

Table 1
Synthesis parameters used and reaction efficiency (RE) in the preparation of starch maleate monoester samples.

Sample	Molar ratio[a]	Volume of water (mL)	DS[b]	RE[c] (%)
1	1:3:1	10	0.21	7.0
2	1:1.5:1	10	0.11	7.3
3	1:0.75:0.5	10	0.12	16.0
4	1:1.5:0.25	10	0.07	4.7
5	1:1.5:0.25	50	0.03	2.0
6	1:1.5:0.25	100	0.04	2.7
7	1:0:0.25	10	–	

[a] Molar ratio of anhydroglucose unit:maleic anhydride:sodium hydroxide.
[b] Degree of substitution (DS) of starch-maleate based on duplicate samples.
[c] Reaction efficiency (RE) was calculated based on the following equation:

$$\mathrm{RE}(\%) = \frac{\mathrm{DS} \times \text{mole of anhydroglucose unit}}{\text{mole of maleic anhydride}} \times 100.$$

3.2. Effect of synthesis parameters

The degree of substitution (DS) of SM sample is defined as the fraction of substituted AGU regardless of whether single or multiple substitution have occurred (Besheer, Hause, Kressler, & Mader, 2007). The DS could be determined from the carboxyl content of the maleate moiety substituted onto the starch chains. The percentage of SM with carboxylic end group was determined by dissolving a given amount of sample in NaOH solution of known concentration and the amount of excess NaOH was back titrated with HCl. As shown in Table 1, SM gels of DS within the range of 0.03–0.21 were prepared in the present study. Samples of SM gel with moderate DS were subsequently subjected to UV irradiation to obtain cross-linked starch-maleate monoester gel particles (CSM). Our synthesis approach differed considerably from most previously reported works which involved the use of aprotic solvents in the esterification of starch in order to obtain high DS (Yoshimura et al., 2006). In the present study, the formation of diester was deemed unlikely due to the short reaction time between hydroxyl groups of starch and maleic anhydride used (Sun & Sun, 2002). The presence of excess water could have led to the formation of starch-maleate monoester samples with lower DS value (sample 6). Reducing the amount of water through evaporation at the reaction temperature of 100 °C would prevent the hydrolysis of SM products formed. However, it would be difficult to obtain a homogeneous mixture from the highly viscous gelatinized starch solution formed at exceedingly low amount of water under alkaline condition. Such high viscosity of alkaline gelatinised starch solution was attributed to increased intermolecular hydrogen bonding between starch chains. Upon addition of maleic anhydride, the resulting reaction mixture of substantially reduced viscosity would readily promote the homogenous substitution reaction. In this study, the reaction

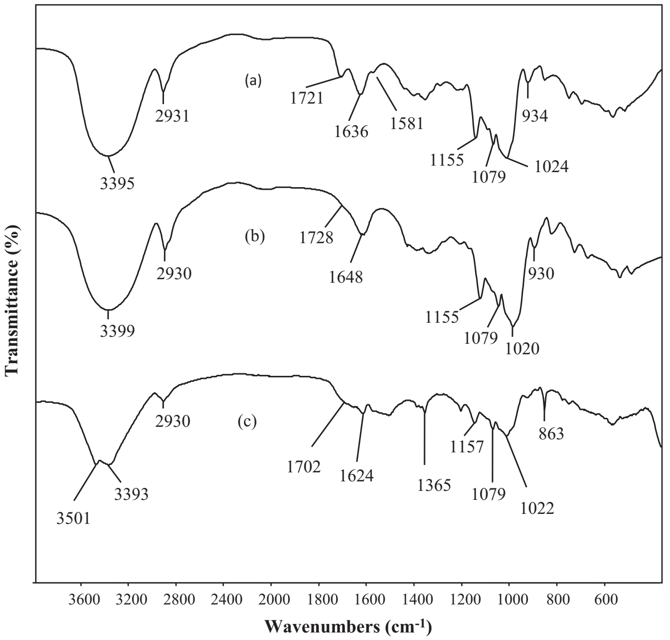


Fig. 3. FTIR spectra of starch-maleate monoester (DS = 0.21) precipitated in different precipitating media (a) ethanol, (b) ethanol:butan-1-ol (1:1), and (c) propan-2-ol.

efficiency (RE) of starch maleate substitution reaction was observed to vary between 2.0% and 16.0% (Table 1).

3.3. *Effect of precipitating media*

FTIR spectra of SM samples precipitated in different media were shown in Fig. 3. The chemical composition and structure of SM gels formed were observed to be influenced by the nature of precipitating media used. SM gels precipitated in ethanol showed a comparatively more distinctive carbonyl peak at 1721 cm^{-1} as compared to samples precipitated in butan-1-ol or propan-2-ol. The relative abundance of substituted amylose and amylopectin components of SM gels being precipitated in various types of alcohol could be associated with different DS of maleic anhydride onto both components of starch. Our findings concurred with results reported by Tang, Mitsunaga, and Kawamura (2006) that the structural composition of starch-based materials precipitated in a mixture of iso-amyl alcohol and butan-1-ol was different from those precipitated in butan-1-ol alone.

3.4. *Moisture absorbency of SM*

In general, the introduction of hydrophilic carboxylic groups onto the molecular structure of starch molecules is expected to alter its water absorbency. Fig. 4 shows the effect of DS on the moisture absorbency of SM samples after being equilibrated at a relative humidity of 100% for 6 days. The rates of water absorption by SM samples were observed to be relatively faster initially, but slowed down gradually with passage of time. All SM samples were observed to exhibit very similar pattern of increasing water absorbency with equilibration duration. Generally, the water absorbency of SM samples of low DS values (DS < 0.03) was observed to be substantially lower than SM samples of higher DS values (DS > 0.08). SM sample of DS 0.21 showed consistently lower moisture absorbency than SM sample of DS 0.08, but higher moisture absorbency than SM sample of DS < 0.03. The carboxylate groups had been shown to play an important role in water absorption as compared to the hydroxyl groups of the starch chains. At low DS, the effect of carboxylate groups on the moisture absorbency of SM samples was not significant compared to hydroxyl groups. The observed lower water absorbency for SM sample of DS 0.21 could be due to its overall reduced hydropilicity at increased substitution of maleate moieties, each of which contained an unsaturated double bond. The formation of extensive intramolecular hydrogen bonding by carboxylate groups of SM monoester chains at higher DS could also have contributed to the observed lower water absorbency.

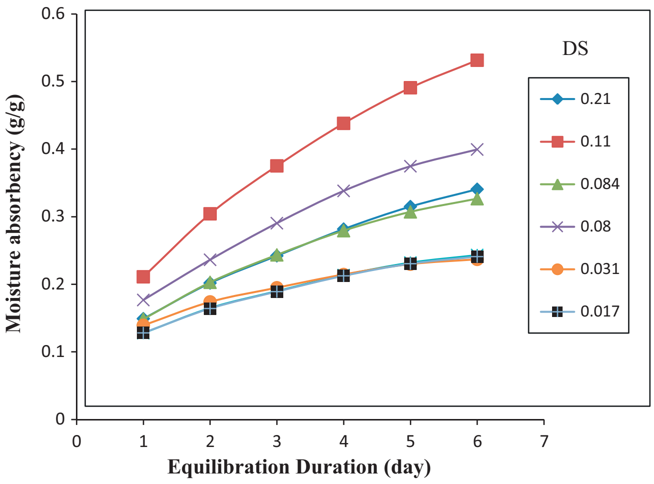


Fig. 4. Effect of degree of substitution (DS) on the moisture absorbency of starch-maleate monoester (precipitated in ethanol) with duration of equilibration at relative humidity of 100%.

3.5. *Effect of UV irradiation*

As SM gel sample is very soluble in water, an aqueous solution of SM can be directly irradiated with UV light under controlled conditions. Partial hydrolysis of the SM sample was evidenced by the reduced intensity of the absorption peak at 1721 cm^{-1} which could be attributed to increased temperature during UV irradiation (Fig. 5). The occurrence of a shoulder at 2860 cm^{-1} adjacent to the absorption peak at 2931 cm^{-1} could be attributed to the methylene C–H stretching band associated with the maleate substituent (Fang et al., 2004). The vinyl moiety of SM could undergo a free

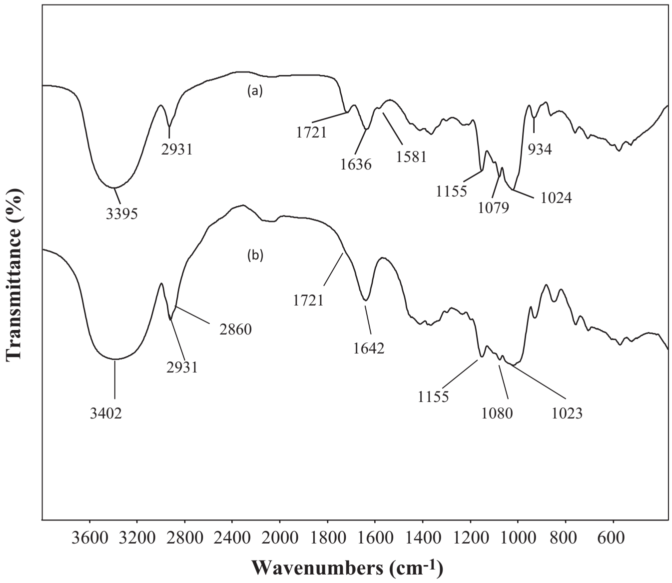


Fig. 5. FTIR spectra of starch maleate monoester (DS = 0.21) (a) before, and (b) after UV irradiation, and precipitated in ethanol.

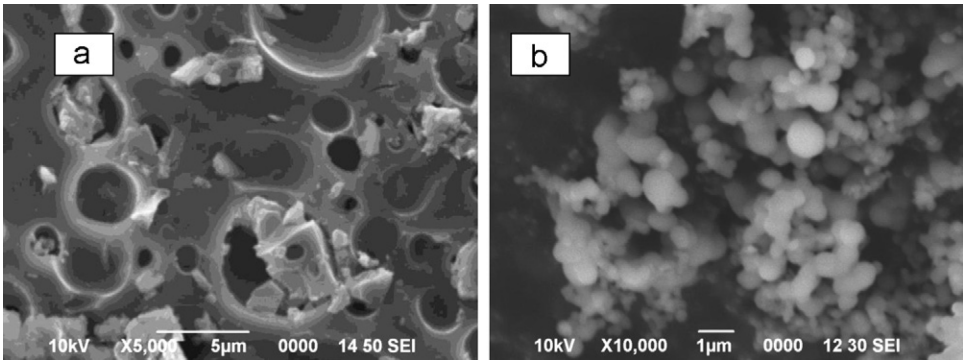
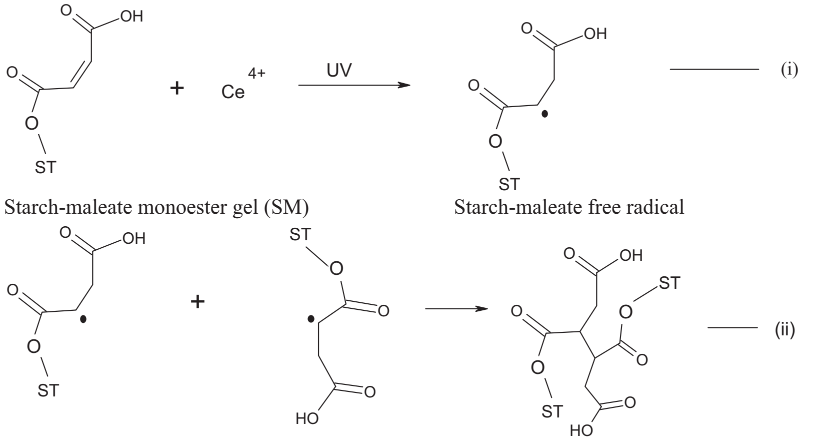


Fig. 6. SEM micrographs of starch maleate monoester (a) before, and (b) after UV irradiation.

radical reaction upon being irradiated with UV light in the presence of cerium(IV) ions which served as the photo-initiator (Alias et al., 2008; Wu, 2003). Based on the reaction mechanism as shown in elementary equation (i), a free radical was formed when the C═C segment of the maleate moiety gained an electron. Two free radicals could then recombine to form a CSM particle as shown in elementary equation (ii).



Starch-maleate monoester gel (SM)

Starch-maleate free radical

Starch-maleate free radicals

Cross-linked starch-maleate gel particles (CSM)

ST = starch

Most starch-based materials show high tendency to form large aggregates of irregular morphology (Alias et al., 2008). The agglomeration characteristics of starch-based materials could be attributed to the hydrophilic nature of the starch chains which readily interacted via hydrogen bonding and entangled with each other easily. Self-assembly of polysaccharide molecules in aqueous solution could take place via hydrogen bonding to form aggregates of different sizes (He, Fu, Shen, & Ghao, 2008). However, the agglomerate size could be influenced by the polarity and the hydrophilic/hydrophobic balance of the polymer backbone. As reported by Henize, Michealis, and Hornig (2007), the introduction of hydrophobic moiety such as perpropionylated group onto dextran furoate pyroglutamate would lead to reduction in the particle size. It was observed that exposure to UV irradiation could induce transformation in the morphology of SM sample from its continuous gel matrix (Fig. 6a) to individual discrete submicron-sized particles (Fig. 6b) of spherical shape, and an unimodal particle size distribution of mean diameter of 445 ± 115 nm (Fig. 7). Such unimodal particle size distribution of CSM particles could be a result of self-aggregation in aqueous solution. CSM particles formed by UV irradiation possessed lower hydrophilicity, and the resulting reduced interactions between particles via hydrogen bonding would therefore lead to the formation of spherical and submicron-sized aggregates of CSM particles.

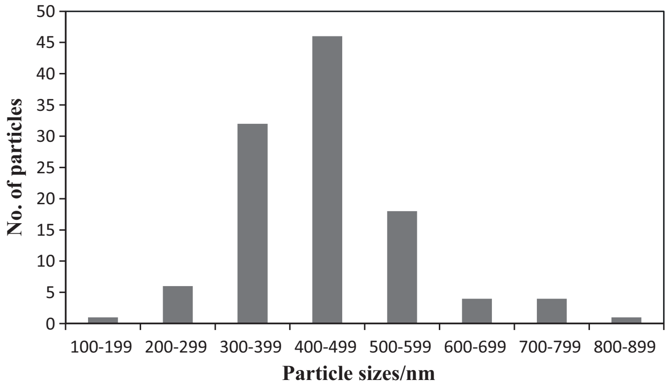


Fig. 7. Histogram showing the size distribution of spherical CSM gel particles (DS = 0.21) formed after UV irradiation.

4. Conclusion

In conclusion, we have reported the facile and green synthesis of starch-maleate monoester gels (SM) and cross-linked starch-maleate gel particles (CSM) with DS within the range of 0.03–0.21 by reacting maleic anhydride with native sago starch in aqueous medium. In this synthesis approach, water and alcohols were used as the solvent and the precipitating media, respectively, whereas UV light irradiation was used to initiate the cross-linking of SM gels. The water absorbency and hydrophilicity of SM samples of low DS values (DS < 0.03) was substantially lower than SM samples of higher DS values (DS > 0.08). The nature of precipitating media could also affect the structural composition of SM gels formed. Controlled UV light irradiation could transform SM gels into submicron-sized spherical aggregates of CSM particles. Being non-toxic, biocompatible and cheap, the high potential utility of CSM particles as drug delivery carriers in biomedical applications is therefore envisaged.

Acknowledgements

The authors wish to thank Ting Woei for her skill assistance in carrying out the SEM work. Financial support from Universiti Malaysia Sarawak (Research grant No.: D1/09/2008(17)) and scholarship from Ministry of Education Malaysia are gratefully acknowledged.

References

Alias, J., Silva, I., Goni, I., & Gurruchaga, M. (2008). Hydrophilic amylose-based graft copolymers for controlled protein release. *Carbohydrate Polymers*, *74*(1), 31–40.

Arnal, M. L., Matos, N. E., Morales, R. A., Santana, O. O., & Müller, A. J. (1998). Evaluation of the fractionated crystallization of dispersed polyolefins in a polystyrene matrix. *Macromolecular Chemistry and Physics*, *199*, 2275–2298.

Besheer, A., Hause, G., Kressler, J., & Mader, K. (2007). Hydrophobically modified hydroxyethyl starch: Synthesis, characterisation and aqueous self-assembly into nano-sized polymeric micelles and vesicles. *Biomacromolecules*, *8*(2), 359–367.

Biswas, A., Shogren, R. L., Kim, S., & Willett, J. L. (2006). Rapid preparation of starch maleate half-esters. *Carbohydrate Polymers*, *64*(3), 484–487.

Bravo-Osuna, I., Ferrero, C., & Jiménez-Castellanos, M. R. (2008). Drug release behaviour from methyl methacrylate-starch matrix tablets: Effect of polymer moisture content. *European Journal of Pharmaceutics and Biopharmaceutics*, *69*(1), 285–293.

Chen, L., Li, X., Li, L., & Guo, S. (2007). Acetylated starch-based biodegradable materials with potential biomedical application as drug delivery systems. *Current Applied Physics*, *7S1*, e90–e93.

Chi, H., Xu, K., Wua, X., Qiang Chen, Q., Xue, D., Song, C., et al. (2008). Effect of acetylation on the properties of corn starch. *Food Chemistry*, *106*(3), 923–928.

Desai, K. G. (2007). Properties of tableted high-amylose corn starch–pectin blend microparticles intended for controlled delivery of diclofenac sodium. *Journal of Biomaterials Applications*, *21*(3), 217–233.

Elfstrand, L., Eliasson, A.-C., Jonsson, M., Reslow, M., Thelin, B., & Wahlgren, M. (2007). Recrystallization of waxy maize starch during manufacturing of starch microspheres for drug delivery: Optimisation by experimental design. *Carbohydrate Polymers*, *68*(3), 568–576.

Elvira, C., Mano, J. F., San Roman, J. S., & Reis, R. L. (2002). Starch-based biodegradable hydrogels with potential biomedical applications as drug delivery systems. *Biomaterials*, *23*(9), 1955–1966.

Fang, J. M., Fowler, P. A., Sayers, C., & Williams, P. A. (2004). The chemical modification of a range of starches under aqueous reaction conditions. *Carbohydrate Polymer*, *55*(3), 283–289.

Gunaratne, A., & Corke, H. (2007). Influence of prior acid treatment on acetylation of wheat, potato and maize starches. *Food Chemistry*, *105*(3), 917–925.

He, Y., Fu, P., Shen, X., & Gao, H. (2008). Review: Cyclodextrin-based aggregates and characterization by microscopy. *Micron*, *39*(5), 495–516.

Henize, Th., Michealis, N., & Hornig, St. (2007). Reactive polymeric nanoparticles based on unconventional dextran derivatives. *European Polymer Journal*, *43*(3), 697–703.

Kacurakova, M., & Wilson, R. H. (2001). Developments in mid-infrared FT-IR spectroscopy of selected carbohydrates. *Carbohydrate Polymers*, *44*(4), 291–303.

Liou, F. I., & Wang, Y. J. (1996). Preparation and characterisation of cross-linked and heat-treated PVA-MA films. *Journal of Applied Polymer Science*, *59*(9), 1395–1403.

Liu, J., Chen, L., Li, L., Hu, X., & Cai, Y. (2004). Steady-state fluorescence study on release of camptothecin from agar hydrogel. *International Journal of Pharmaceutics*, *287*(1–2), 13–19.

Mahmoudi, M., Simchi, A., Imani, M., & Hafeli, U. O. (2009). Superparamagnetic iron oxide nanoparticles with rigid cross-linked polyethylene glycol fumarate coating for application in imaging and drug delivery. *Journal of Physical Chemistry C*, *113*(19), 8124–8131.

Mulhbacher, J., Ispas-Szabo, P., Ouellet, M., Alex, S., & Mateescu, M. A. (2006). Mucoadhesive properties of cross-linked high amylose starch derivatives. *International Journal of Biological Macromolecules*, *40*(1), 9–14.

Pang, S. C., Chin, S. F., Tay, S. H., & Tchong, F. M. (2011). Starch–maleate–polyvinyl alcohol hydrogels with controllable swelling behaviors. *Carbohydrate Polymers*, *84*(1), 424–429.

Pal, K., Banthia, A. K., & Majumdar, D. K. (2008). Effect of heat treatment of starch on the properties of the starch hydrogels. *Materials Letters*, *62*(2), 215–218.

Raquez, J.-M., Nabar, Y., Srinivasan, M., Shin, B.-Y., Narayan, R., & Dubois, P. (2008). Maleated thermoplastic starch by reactive extrusion. *Carbohydrate Polymers*, *74*(2), 159–169.

Rivero, I. E., Balsamo, V., & Müller, A. J. (2009). Microwave-assisted modification of starch for compatibilizing LLDPE/starch blends. *Carbohydrate Polymers*, *75*(2), 343–350.

Roesser, D. S., McCarthy, S. P., Gross, R. A., & Kaplan, D. L. (1996). Effects of substitution site on acetyl amylose biodegradability by amylase enzyme. *Macromolecules*, *29*(1), 1–9.

Shanbhag, A., Barclay, Br., Koziara, J., & Shivanand, P. (2007). Application of cellulose acetate butyrate-based membrane for osmotic drug delivery. *Cellulose*, *14*(1), 65–71.

Sun, R., & Sun, X. F. (2002). Succinoylation of sago starch in the N,N-dimethylacetamide/lithium chloride system. *Carbohydrate Polymers*, *47*(4), 323–330.

Tang, H., Mitsunaga, T., & Kawamura, Y. (2006). Molecular arrangement in blocklets and starch granule architecture. *Carbohydrate Polymers*, *63*(4), 555–560.

Thakur, S., Chauhan, G. S., & Ahn, J.-H. (2009). Synthesis of acryloyl guar gum and its hydrogel materials for use in the slow release of L-DOPA and L-tyrosine. *Carbohydrate Polymers*, *76*(4), 513–520.

Tiyaboonchai, W. (2003). Chitosan nanoparticles: A promising system for drug delivery. *Naresuan University Journal*, *11*(3), 51–66.

Wang, Y.-J., & Wang, L. (2002). Characterization of acetylated waxy maize starches prepared under catalysis by different alkali and alkaline earth hydroxides. *Starch-Stärke*, *54*(1), 25–30.

Wu, C.-S. (2003). Physical properties and biodegradability of maleated-polycaprolactone/starch composite. *Polymer Degradation and Stability*, *80*(1), 127–134.

Xu, Y., Miladinov, V., & Hanna, M. A. (2004). Synthesis and characterisation of starch acetates with high substitution. *Cereal Chemistry*, *81*(6), 735–740.

Yoshimura, T., Yoshimura, R., Seki, C., & Fujioka, R. (2006). Synthesis and characterization of biodegradable hydrogels based on starch and succinic anhydride. *Carbohydrate Polymers*, *64*(2), 345–349.