

Microwave Assisted Synthesis and Evaluation of Cross-Linked Carboxymethylated Sago Starch as Superdisintegrant

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ABSTRACT

The aim of this study was to modify the sago starch and evaluate its efficacy as tablet disintegrant. Cross-linked carboxymethylated sago starch (CMSS) was synthesized using native sago starch (SS) and monochloroacetic acid (MCA) with sodium hydroxide in microwave radiation environment. FT-IR analysis of the sample confirmed the carboxymethylation by showing absorption peak at 1607.2 cm⁻¹. CMSS with degree of substitution (DS) of 0.31 was formed and, it was further evaluated as disintegrant in Ondasetron based tablets. The results revealed that CMSS could be used as disintegrant in tablet formulation in concentration dependant manner.

Keywords: Sago Starch, Carboxymethylation, Disintegrant, SEM, FT-IR

1. Introduction

Starch is one of the most important and abundant plant polysaccharide next to cellulose and chitin. Starch is found primarily in the seeds, fruits, tubers, and stem pith of plants, most notably corn, wheat, rice, sago, and potatoes. Starch derivatives play vital roles in the promising biopolymers industries. This is because they are cheap, non-toxic, renewable and biocompatible with many other materials for industrial applications. Starches are employed in food, pharmaceutical and allied industries because of its good thickening and gelling properties. Starches can be modified by chemical, physical and enzymatic methods for their tailor made use in different form [1]. They are mainly used as binder, filler, emulsion stabilizer, consistency modifier and disintegrantss. Crosslinked sodium carboxymethyl starch which is also known as sodium starch glycolate is extensively used in fast dissolving tablets to disperse the drugs within short span of time and deliver the active drug in the systemic circulation of the body.

In a number of earlier reported methods, carboxymethylation of starch has been done using strong NaOH and Mono chloroacetic acis (MCA) in aqueous/organic medium at elevated temperature. It has been shown that when a mixture of starch with sodium hydroxide and

monochloroacetic acid is irradiated, the carboxymethyl starch obtained consists of fractions with high levels of carboxymethyl groups and fractions with a predominant content of carbonyl groups [2]. Earlier some workers have modified yam starch and evaluated its efficacy as tablet disintegrant [3]. In our laboratory recently we have synthesized carboxymethylated derivative of moth bean starch by conventional method and evaluated as superdisintegrant [4]. Microwave assisted synthesis is an efficient and novel technique used in polymer synthesis. Microwave-assisted synthesis has attracted huge interest in recent years among researchers due to its rapid transfer of energy in the bulk of the reaction, as well as short reaction time. Compared with the conventional approach a microwave-assisted reaction has advantages of energy saving, high conversion, and rapidity [5,6].

The sago palm (*Metroxylon sagu* Rottb.) is grown well in the tropical rain forests of Southeast Asia. This palm contains nearly 20-45% starch on dry weight basis in its trunk and it is one of the potential underutilized palms [7].

This study was designed to synthesize the crosslinked carboxymethyl derivative of sago starch, and evaluate its efficacy as disintegrant in pharmaceutical formulation. Ondasetron was chosen as model drug.

2. Material and Methods

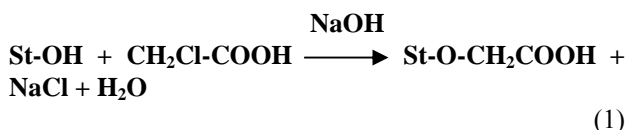
2.1. Materials

Sodium starch glycolate and POCl_3 was procured from Lobachemie, India. Ondasetron HCl was kindly donated by Comed Pharmaceuticals Limited, Baddi, India. Monochloro acetic acid (CDH, India) and Sodium hydroxide (Merck, India) were procured and used without further purification. Sago starch was procured from local market of Chennai, Tamilnadu, India. All other chemicals received were of AR grade and used without further purification.

2.2. Methods

2.2.1. Modification of Sago Starch

Carboxymethylation of Sago starch (SS) was carried out by following slight modified method described elsewhere [8-10]. In this method Sago starch (4 g), NaOH (3.2 g) and monochloroacetic acid (4 g) were taken in a beaker, with 20 ml of Isopropyl alcohol and water (50:50) and the contents were subjected to continuous stirring to homogeneity. Subsequent reaction was allowed to proceed at varying temperature (from 25°C to 70°C and duration of reaction (from 1 to 4 min) in the Microwave oven (Model No.CE1111TL, Samsung Electronics, India). The reaction products were precipitated with ethanol and washed alkali free and dried in a vacuum oven at 45°C for 8 h. The reaction takes place in following manner:



Finally dried powder was further cross-linked with Phosphorous oxychloride (POCl_3) to get the cross-linked Na-carboxymethylated sago starch (CMSS).

2.2.2. Degree of Substitution

The DS of carboxymethylated sago starch (CMSS) was determined by the method reported elsewhere [11]. The carboxymethyl groups in the CMSS were first converted to an acid form with acid (HCl). The acidified starch was then recovered by precipitation with methanol, filtration, washing with methanol, and drying. Then, 0.2 M NaOH (20 ml) was added to a suspension of accurately weighed CMSS in 30 ml of purified water. The mixture was transferred to a 100-ml volumetric flask and adjusted to the mark with purified water. The solution (25 ml) was transferred to an Erlenmeyer flask and titrated with 0.04 M HCl using phenolphthalein as the indicator. The titration was repeated three times, and the average value of HCl volume was used for the calculations. A blank was also titrated. The DS was calculated using following equations:

$$\text{Degree of substitution} = \frac{162 \times n\text{COOH}}{\text{MDS-58} \times n\text{COOH}} \quad (2)$$

$$\text{MDS} = \frac{(1 - W_{\text{water}})}{100} \times \text{MS} \quad (3)$$

$$n\text{COOH} = (V_b - V) \times C_{\text{HCl}} \times 4 \quad (4)$$

where 162 is the molar mass of AGU (g/mol); nCOOH (mol) is the amount of COOH; MDS (g) is the mass of dry sample; MS (g) is sample mass; W_{water} (%) is the water content; V_b (ml) is the volume of HCl used for the titration of the blank; V (ml) is the volume of HCl used for the titration of the sample; C_{HCl} (mol/L) is the HCl concentration.

2.2.3. Scanning Electron Microscopy

Each starch samples were firstly air dried, and then coated with gold. The prepared starch samples were viewed under scanning electron microscope (JEOL, Japan).

2.2.4. FT-IR Study

Both native and carboxymethylated starch sample (5 mg) were blended with solid KBr, (Merck, Germany) and about 40 mg blend was used to prepare a pellet (Hydraulic pellet press KP, Mumbai, India). The spectra were scanned from $4000\text{-}400\text{ cm}^{-1}$ in a Perkin Elmer FT-IR spectrometer (Perkin Elmer, USA) under dry air at room temperature.

2.2.5. Swelling Capacity

The swelling capacity of the native SS, CMSS and SSG was estimated by slightly modified method of [12]. In this method the tapped volume occupied by 10 gm of the powder (V_x), was noted and the powder was dispersed in 85 ml of distilled water and the volume made up to 100 ml with distilled water. After 24 h of standing, the volume of the sediment (V_s) was measured. The swelling capacity was then computed as the ratio of V_s/V_x .

2.2.6. Hydration Capacity

The slight modified method [13] was used for this study. A 10 gm was placed in each of four 15 ml plastic centrifuge tubes to which 10 ml of distilled water was added and then stoppered. The contents were mixed on a cyclomixer for 2 min. The mixture was allowed to stand for 10 min and then centrifuged at 1000 rpm for 10 min on absented centrifuge.

The supernatant was carefully decanted, and the sediment was weighed. The hydration capacity (Hc) was then calculated using the equation:

$$\text{Hc} = \frac{\text{Sediment weight}}{\text{Dry sample weight}} \quad (5)$$

2.2.7. Viscosity Determination

Viscosity of all the samples were carried out using Brookfield Viscometer (Brookfield Engineering Laboratory, USA) at 25°C, using spindle no 92 at 6 rpm h⁻¹. The concentration of all the samples were kept at 10%w/v.

2.2.8. Tablet Formulation

Eight batches of the tablets were prepared using direct compression method. Four batches (F1-F4) contain CMSS; and other four (F5-F8) contains SSG as superdisintegrant in the ratio of 2, 4, 6 and 8%w/w respectively. All ingredients were mixed properly and then powder blend was compressed into tablets using a ten-station tablet compression machine (Shakti Engineering, Ahmedabad, India).

2.2.9. Evaluation of Tablets

All the tablets were evaluated for hardness, friability, drug content and percentage weight variation. To evaluate the efficiency of carboxymethylated sago starch as disintegrant in pharmaceutical formulation, the synthesized CMSS was evaluated and compared with established superdisintegrant *i.e.* Sodium starch glycolate at 2, 4, 6 and 8% w/w concentration as disintegrant in Ondasetron based tablets. The *in vitro* disintegration study was carried out using USP disintegration apparatus (Tab Machine, Mumbai, India).

3. Results and Discussions

Carboxymethylated sago starch with different DS was prepared using MCA and sodium hydroxide in reaction medium of isopropyl alcohol/water. The optimization of carboxymethylation reaction was performed by varying two reaction parameter *i.e.* reaction temperature and duration of reaction. Each parameter is varied keeping other constant. The influence of these parameters on DS was followed experimentally.

3.1. Influence of Temperature and Duration of Reaction on Carboxymethylation

The influence of reaction temperature on DS is shown in **Figure 1**. The DS of CMSS increases with varying the temperature. The highest DS value (0.31) was obtained at 55°C and it decreases further, this could be due to change in its confirmation or, due to degradation. Further all investigations were carried out at 55°C, since it produced highest DS.

The duration of reaction was varied from 1 to 4 min. The value of DS obtained at different time points are shown in **Figure 2**. It can be seen that DS value increases with reaction time and further decreases, it might be due to degradation of this polymer. The surface texture of the sago starch is somewhat oval shaped (**Figure 3**) but after

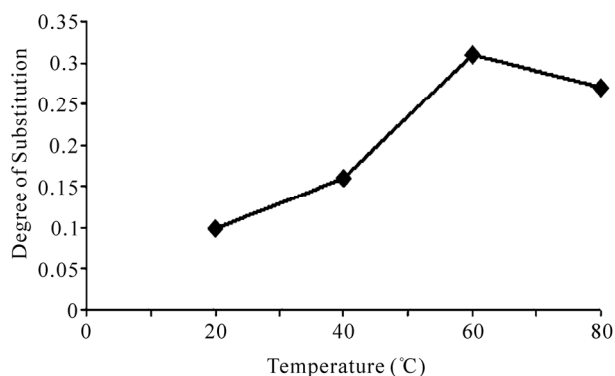


Figure 1. Influence of reaction temperature on DS.

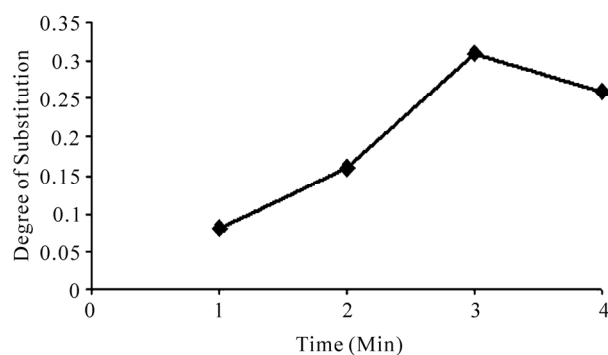


Figure 2. Influence of duration of reaction on DS.

cross-linking the surface texture has been somewhat disoriented that can be seen in **Figure 4**.

3.2. Physicochemical Character

The addition of carboxyl group is indicated by presence of an absorption peak band at 1607.2 in the FT-IR spectrum of CMSS which is not present in native sago starch (shown in **Figure 5**). The swelling power of the starches is presented in **Table 1**. The decreasing order of the swelling power was SSG \approx CMSS > SS. The Swelling power of the starches was due to the amylopectin portion and concentration in the starch granules. Water penetration into the starch granules may be increased due to hydrophilic nature of carboxymethyl group, which resulted into swelling of the starch granules, and dissolution in water. Carboxymethylation decreases the amylose content in starch by destruction of helical structure of amylose. Similarly comparative hydration capacity is shown in **Table 1**, SSG had high hydration capacity as compared to CMSS and SS. This may be due to different DS value of carboxymethylation and amylose/amylopectin ratio and arrangement in starch. The hydration value of CMSS and SSG is more as compared to SS; it may be due to addition of negatively charged carboxymethyl group as well as alkalization of starch [14].

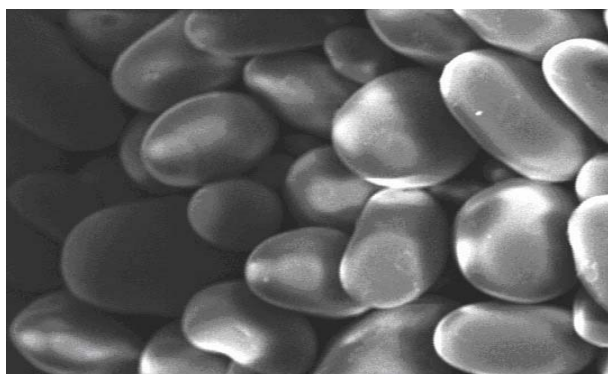


Figure 3. Scanning electron micrograph of native sago starch.

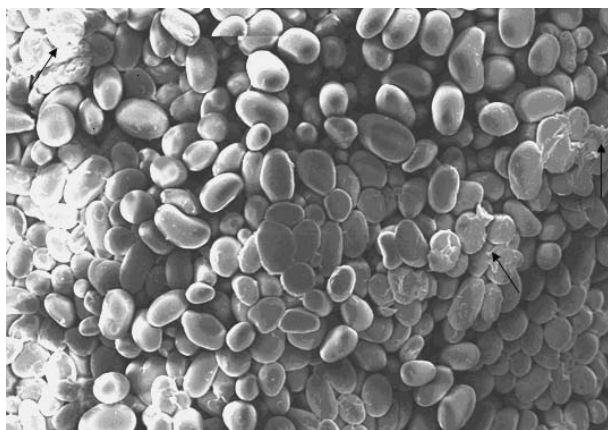


Figure 4. Scanning electron micrograph of carboxymethylated sago starch.

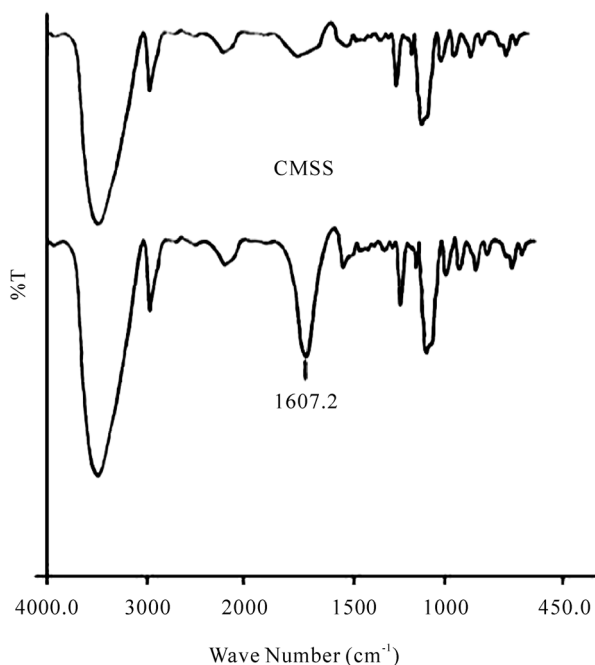


Figure 5. FT-IR spectra of native and modified sago starch.

3.3. Tablet Evaluation

All the prepared tablets were evaluated for physical characterization and data shown in **Table 2**. The results were found within the official limits. Tablets containing different concentration of CMSS and SSG were evaluated for disintegrant property (shown in **Figure 6**). Carboxymethylation of starch increases its cold-water hydrophilicity due to addition of negatively charged functional group (CH_2COO^-) in the parent chain of native starch. The less concentration of CMSS possesses insufficient swelling power to break the tablets. The tablets containing higher conc. (6% w/w) CMSS showed nearly comparable disintegration time as shown by SSG based tablets. At higher conc. (8% w/w) the disintegration time of both the tablets, mainly SSG based was decreased that may be due to formation of viscous gel mass which impede the penetration of water in to the tablets and retarded the disintegration power. The use of CMSS as a tablet disintegrant in this study seemed to have the optimum concentration at 8 %w/w.

Table 1. Comparative swelling, hydration and viscosity behavior of all starches.

| Starch Type | Swelling capacity | Hydration capacity | Viscosity (cps) |
|-------------|-------------------|--------------------|-----------------|
| Sago Starch | 1.6 ± 0.10 | 0.68 ± 0.15 | 61343 |
| CMSS | 4.0 ± 0.21 | 2.2 ± 0.10 | 74012 |
| SSG | 4.2 ± 0.25 | 2.4 ± 0.25 | 75643 |

All the values are represented as Mean \pm SD; and n = 3.

Table 2. Physical Evaluation of tablets.

| Batch | Hardness (kg/cm ²) | Friability (%) | Drug content (%) | % Weight deviation |
|-------|--------------------------------|-----------------|------------------|--------------------|
| F1 | 4.6 ± 0.25 | 0.35 ± 0.26 | 97.35 ± 0.35 | 1.3 ± 0.18 |
| F2 | 4.7 ± 0.37 | 0.33 ± 0.15 | 98.26 ± 0.20 | 1.0 ± 0.28 |
| F3 | 4.3 ± 0.26 | 0.44 ± 0.21 | 99.13 ± 0.21 | 2.5 ± 0.20 |
| F4 | 5.2 ± 0.31 | 0.53 ± 0.40 | 98.33 ± 0.26 | 2.7 ± 0.15 |
| F5 | 4.9 ± 0.25 | 0.34 ± 0.35 | 99.43 ± 0.23 | 2.1 ± 0.35 |
| F6 | 5.0 ± 0.22 | 0.22 ± 0.25 | 97.32 ± 0.20 | 2.4 ± 0.14 |
| F7 | 5.2 ± 0.30 | 0.39 ± 0.16 | 98.48 ± 0.30 | 2.9 ± 0.20 |
| F8 | 5.1 ± 0.10 | 0.36 ± 0.24 | 97.98 ± 0.34 | 2.1 ± 0.12 |

All the values are represented as Mean \pm SD; and n = 3.

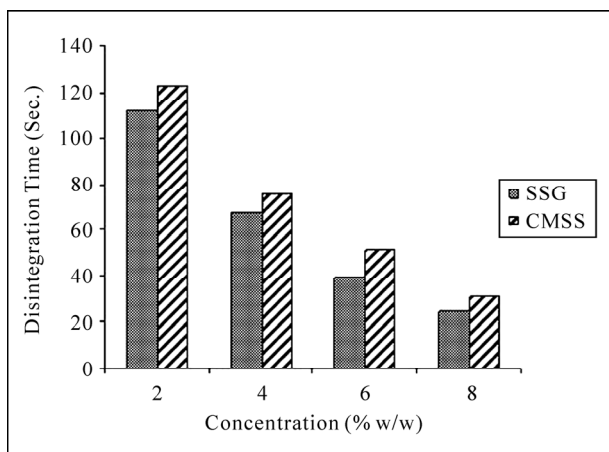


Figure 6. Comparative disintegration behavior in ondasetron based tablets.

4. Conclusion

CMSS was synthesized in microwave radiation environment with DS value of 0.31 using MCA and NaOH in IPA/H₂O solvent medium. The physicochemical values are comparable to official superdisintegrant *i.e.* SSG, but much higher than native sago starch. CMSS could be used as a potential disintegrant in tablet dosage form at higher concentration (8% w/w).

5. Acknowledgement

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