



ORIGINAL ARTICLE

# Synthesis and evaluation of the structural and physicochemical properties of carboxymethyl pregelatinized starch as a pharmaceutical excipient



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**Abstract** A pregelatinized starch (PGS) was derivatized with sodium chloroacetate (SCA) in alcoholic medium under alkaline condition to produce carboxymethyl pregelatinized starch (CMPGS) with various degrees of substitution (DS). Influence of the molar ratio of SCA to the glucopyranose units (SCA/GU), reaction time, temperature and the amount of sodium hydroxide on the degree of substitution (DS) and the reaction efficiency (RE) was studied. An optimal concentration of 30% of NaOH, for a reaction time of 1 h at 50 °C and molar ratio (SCA/GU) equal to 1.0, yielded an optimal DS of 0.55 and a RE of 55%. SEM micrographs revealed that the carboxymethylation assigned the structural arrangement of CMPGS and caused the granular disintegration. Wide angle diffraction X-ray (XRD) showed that the crystallinity of starch was obviously varied after carboxymethylation. New bands in FTIR spectra at 1417 and 1603  $\text{cm}^{-1}$  indicated the presence of carboxymethyl groups. The solubility and viscosity of CMPGS increased with an increase in the degree of modification. In order to investigate the influence of DS on physical and drug release properties, CMPGS obtained with DS in the range of 0.12–0.55 was evaluated as tablet excipient for sustained drug release. Dissolution tests performed in phosphate buffer (pH 6.8), with Ibuprofen as drug model (25% loading) showed that CMPGS seems suitable to be used as sustained release excipient since the drug release was driven over a period up to 8 h. The in vitro release kinetics studies revealed that all formulations fit well with Korsmeyer-Peppas model and the mechanism of drug release is non-Fickian diffusion.

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## 1. Introduction

Starch is, after cellulose, the main carbohydrate substance synthesized by higher plants. The most important sources of starch are represented by cereals, tubers and legumes. Some fruits are also rich in starch. In the native state, starch is

insoluble in cold water and consists of granules whose size, composition, physicochemical and functional properties depend on the botanical origin (Rahman, 2007) and culture conditions (Jaisut, 2008). These properties, however, can change depending on the treatment to which the granules are subjected.

Starches are mainly used in oral solid dosage forms as fillers, binders or disintegrants. However they have some limitation properties. To improve their properties such as flowability, gelatinizing temperature, gel viscosity, hydrophilicity, or swelling characteristic, starches have been modified. Modifications including physical, chemical and genetic modification were introduced as matrices forming excipients for oral sustained-release dosage forms (Clausen and Bernkop-Schnürch, 2001; Chebli et al., 2001; Mulhbacher et al., 2004; Yoon et al., 2007; Odeku et al., 2008).

Pregelatinized starch (PGS) is obtained by gelatinizing and drying of starch suspension. Gelatinization is a process involving the transformation of an aqueous starch suspension into a starch paste. PGS is characterized by a marked swelling in contact with cold water; it presents an excellent wettability and an easy dispersion in cold water (Anastasiades et al., 2002). Among the derivatives of starch, PGS is more commonly used in pharmaceutical industry (Pifferi et al., 1999). It is used as a hydrophilic excipient for the formulation of sustained release in solid dosage forms (Te Wierik et al., 1997; Van der Voort Maarschalk et al., 1997).

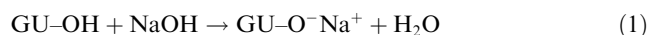
Pregelatinized maize starch is physically modified maize starch with main advantages such as cold water solubility, high viscosity, and moisture sorption and swelling (Odeku et al., 2008). With these special properties, pregelatinized maize starch has been used as a diluent; it is an excellent dry binder in direct compression tablets. It provides uniform filling of dies to ensure correct dosage, and has excellent disintegration/dissolution properties (Podczek, 1999; Gohil et al., 2004). The thermally modified starches have given some promising results as hydrophilic matrices for extended release (Sanchez et al., 1995; O'Brien et al., 2009; Peerapattana et al., 2010).

Modified starches have been studied as functional ingredients in sustained release applications because of their improved functionality over their native counterparts (Lenaerts et al., 1998; Mulhbacher et al., 2001; Assaad and Mateescu, 2010). Chemically modified starches retain their macromolecular nature whatever the chemical modification, while presenting a wide range of physicochemical properties (Bhattacharyya et al., 1995). Chemical modification of starch includes a series of reactions causing a change in the chemical structure of some of the glycosyl units starch macromolecules (Garcia et al., 2012). They relate to the primary and secondary alcohol functions of glycosyl units (oxidation, esterification, and etherification), the glycosidic bond and pseudo aldehyde function (hydrogenation). In the particular case of the hydroxyl functions, products from the chemical modification are characterized by their degree of substitution (DS), which represents the average number of substituted functions ( $0 < DS < 3$ ) per glucosidic unit (GU) (Seidel et al., 2004). Each GU contains three hydroxyl groups ( $C_2$ ,  $C_3$ , and  $C_6$ ) and the substitution is in the order  $C_2 > C_6 > C_3$  (Heinze et al., 1999; Volkert et al., 2004).

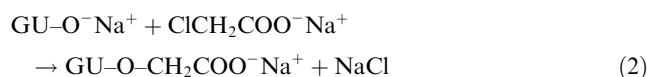
The etherification reaction of starch is one of the methods used to improve the physical and chemical properties of starch (Lawal et al., 2008). Derivatives of etherified starches including carboxymethylated starch have better physicochemical

properties compared to ordinary starch and are generally used as excipients in extended release of drugs (Sangseethong et al., 2005). During the carboxymethylation reaction, hydroxyl groups in the starch molecules are substituted with carboxymethyl groups (Calinescu et al., 2007). They are prepared by a reaction of starch and sodium chloroacetate (SCA) in the presence of sodium hydroxide (NaOH). The process is performed in two steps.

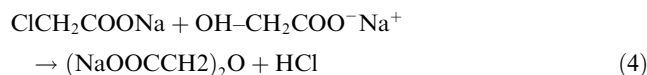
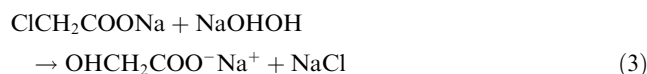
The first step is the reaction where the alkalization of GU-OH group within the PGS molecule are activated and converted into a more reactive alkaline form (GU-O<sup>-</sup>):



In the second step, glucopyranose unit is etherified by carboxymethyl groups (Eq. (2)):



Additionally, two undesirable side reactions can also occur (Eqs. (3) and (4)):



It has been shown by analysis of NMR spectra that the modified starch is preferably made of oxygen bound to carbon 2 by a nucleophilic substitution reaction of order 2 (Massicotte et al., 2008) as shown in Fig. 1.

Several studies have been made on the synthesis of carboxymethyl starches with different types of starches (Noor Fadzlina et al., 2005; Sangseethong et al., 2005; Kamel and Jahangir, 2007; Kittipongpatana et al., 2008; Lawal et al., 2008; Spychaj et al., 2013). Some works have also been carried out to evaluate the effects of reaction parameters on the carboxymethylation of starch such as the concentration of NaOH, amount of etherification agent, and solvent type. The properties of carboxymethyl starches are primarily a low gelatinization temperature and swelling properties and, solubility in cold water than most interesting native starches (Noor Fadzlina et al., 2005). These properties can be characterized by the degree of substitution (DS) or the average number of hydroxyl groups substituted by carboxymethyl groups (Zhou et al., 2007). Most of the commercially produced carboxymethyl corn starches have a degree of substitution (DS) value of less than 0.3 with a high swelling power property, excellent solubility at ambient temperature, low intrinsic viscosity and reduced tendency to retrograde (Bhattacharyya et al., 1995).

In order to avoid gelatinization and keep the granular structure intact, the reaction is usually performed in an organic medium (Heinze et al., 2001; Tijssen et al., 2001a).

In the present work, pregelatinized corn starch (PGS) has been used as raw material to obtain carboxymethyl starch (CMPGS) with a higher DS than other types of native starches. CMPGS was obtained by a reaction between PGS and sodium chloroacetate (SCA) in an alkaline environment. The effects of operating parameters such as the molar ratio of SCA to the glucopyranose units (SCA/GU), reaction time, temperature and the amount of sodium hydroxide on the degree of substitution (DS) and the reaction efficiency (RE) were investigated.

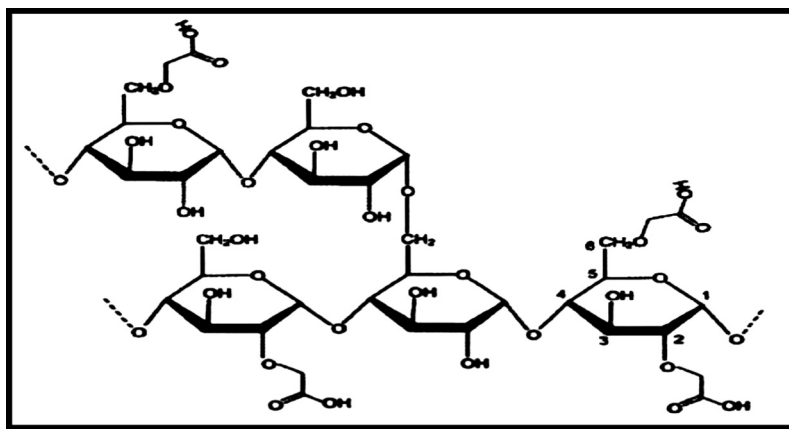


Figure 1 Chemical structure of carboxymethyl starch.

Also, the modified starch (CMPGS) was characterized and used for the preparation of tablet excipients for pharmaceutical uses.

## 2. Materials and methods

### 2.1. Materials

Partially pregelatinized corn starch (PGS) was provided by Polypharma-GMBH (Germany). It contains 28% of amylopectin, 72% of amylose with 20% gelatinization level and 7.2% of moisture content. The particle size is about 65  $\mu\text{m}$ . Sodium chloroacetate (SCA) was supplied by Fluka (USA). Isopropyl alcohol was supplied by Sigma-Aldrich (Germany), sodium hydroxide (NaOH) and hydrochloric acid (HCl) were supplied by Merck (Germany), and glacial acetic acid and methanol (95%) were supplied by Merck (Germany).

### 2.2. Carboxymethylation reaction of pregelatinized starch (PGS)

The synthesis of carboxymethyl starch followed the method of Lazik et al. (2002) with minor modification. PGS (10 g) was weighed in a covered round-bottomed reactor flask equipped with stirrer, reflux-condenser and burette each containing 400 mL of isopropyl alcohol. The reflux-condenser was used to prevent the loss of organic liquid. One hundred milliliters of aqueous NaOH solution at different concentrations ranging from 10–50% w/v was added into the reactor flask over a period of 20 min. The mixture was then stirred for 30 min and SCA was then added in order to obtain different SCA/GU molar ratios (0.2:1, 0.4:1, 0.6:1, 0.8:1, 1:1, 1.2:1 and 1.4:1) in the reaction mixture. Subsequently, the flask was heated to the reaction temperature which varied from 20 to 70  $^{\circ}\text{C}$  for 30 min to 2.5 h. After cooling, the reaction mixture was then neutralized with glacial acetic acid until the pH of about 5.0 was obtained. The CMPGS (Na) was recovered by filtration and washed with a methanol/water (80:20, v/v) solution four times. The purified CMPGS (Na) was then dried in oven for 24 h at 60  $^{\circ}\text{C}$ .

### 2.3. Degree of substitution (DS)

The degree of substitution (DS) of CMPGS (Na) is defined as the average number of carboxymethyl (CM) groups per GU

and lies between 0 and 3. First, it was necessary to convert CMPGS (Na) to the acid form CMPGS (H) by adding 100 mL of acetone and 30 mL of HCl (6 M) to 10 g of CMPGS (Na) under stirring for 120 min (Stojanovic et al., 2005). To remove the excess of acid, CMPGS (H) was treated with the same manner as in the carboxymethylation reaction. The DS is determined by the acid–base titration of a sample of 10 g CMPGS (H), dissolved in 40 mL of NaOH (0.1 M). The resulting solution was diluted to 100 mL with distilled water. Excess NaOH was titrated with a solution of 0.05 M of HCl in the presence of phenolphthalein (Stojanovic et al., 2005). Similarly, a blank, without CMPGS (H) was also titrated. The number of moles of CM groups is given by Eq. (5):

$$n_{\text{-COOH}} = (V_b - V) \cdot C_{\text{HCl}} \quad (5)$$

where  $V_b$  is the volume of HCl used for the titration of the blank,  $V$  is the volume of HCl used for the titration of the sample and,  $C_{\text{HCl}}$  is the concentration of HCl used for the sample titration.

The degree of substitution (DS) is calculated according to the method of Stojanovic et al. (2005) and the reaction efficiency (RE) by the method of Kweon et al. (1996).

$$\text{DS} = \frac{162 \times n_{\text{-COOH}}}{m_{\text{dry}} - 58 \times n_{\text{-COOH}}} \quad (6)$$

where 162 g/mol is the weight of a molar unit of GU, 58 g/mol is the increase in the molecular weight for each CM group substituted,  $m_{\text{dry}}$  is the weight of the anhydrous sample.

$$\text{RE} (\%) = \frac{\text{DS}}{\text{RSMR}} \cdot 100 \quad (7)$$

where the term RSMR represents the reagent/starch molar ratio; it corresponds to the SCA/PGS molar ratio given by:

$$\text{RSMR} = \frac{n_{\text{SCA}}}{n_{\text{GU}}} \quad (8)$$

where  $n_{\text{SCA}}$  is the number of moles of SCA and,  $n_{\text{GU}}$  is the number of moles of GU.

### 2.4. Characterization methods

#### 2.4.1. Fourier transform infrared (FTIR)

The FTIR absorption spectra of PGS and CMPGS were made using the technique of KBr disc (IR spectrophotometer Fourier Transform, Perkin Elmer Precisely, Model Lambda 25).

Before analysis, CMPGS and PGS powders were dried and stored in a desiccator before preparing KBr pellets. Scanning was carried out between 4000 and 400  $\text{cm}^{-1}$  with a step of 4  $\text{cm}^{-1}$  of resolution for each sample.

#### 2.4.2. Scanning electron microscopy (SEM)

Morphology of PGS and CMPGS was studied using a scanning electron microscope (Philips XL 30 ESEM) with tungsten filament, coupled with a complete system of EDS microanalysis X. PGS and CMPGS samples were suspended in ethanol to obtain 1% suspension. One drop of the sample solution was applied on an aluminum stub, and the starch was coated with gold-palladium (60:40). The filament (current around 80  $\mu\text{A}$ ) at acceleration potential of 20.0 kV was used during micrography, with 1000 $\times$  magnification.

#### 2.4.3. X-ray diffraction (XRD)

XRD data were measured at room temperature using a diffractometer (PANalytical: XPERT PRO-) X-ray ceramic tube with copper anticathode using a generator power RX of 20 mA and 40 kV. The diffractometer is equipped with software for data acquisition (Data Collector of PANalytical) and a software for data processing (PANalytical HighScore Plus), providing a  $\text{CuK}\alpha$  radiation ( $\lambda = 1.54 \text{ \AA}$ ). Powder samples were exposed to X-ray beam at 2 $^\circ$ /min.

#### 2.4.4. Evaluation of the rheological properties

The viscosity was determined using a rotational viscometer (Haake Viscotester VT5R, Germany) at shear rates ranged from 10 to 200  $\text{s}^{-1}$  at 25  $^\circ\text{C}$ . Each measurement was performed in triplicate. Samples were prepared with PGS and CMPGS suspension (3% in wt.) in distilled water and placed under magnetic stirring at 80  $^\circ\text{C}$  for 20 min. Thereafter, the solution was kept stirring until it reaches room temperature. The prepared samples were allowed to stand for 24 h before analysis of viscosity.

#### 2.4.5. Analysis of powder properties

The powder flow is an important parameter in the preparation of pharmaceutical solids. It is highly dependent on the particle morphology. Only powder with good flowability reaches uniform dosing in tablet press, by a good material flow from tablet hopper to the die. Flowability can be evaluated by the Hausner ratio (HR) and the compressibility index (CI) also

named Carr index (Carr, 1965; Hausner, 1967) that were respectively calculated using Eqs. (8) and (9) deduced from the USP method (US Pharmacopeia XXXI, 2008).

$$\text{CI} = \frac{\rho_T - \rho_B}{\rho_T} \times 100 \quad (9)$$

$$\text{HR} = \frac{\rho_T}{\rho_B} \quad (10)$$

where  $\rho_B$  is the bulk density and  $\rho_T$  is the tapped density ( $\text{g}/\text{m}^3$ ).

The bulk density ( $\rho_B$ ) and tapped density ( $\rho_T$ ) of PGS and CMPGS powders were determined according to the USP method (US Pharmacopeia XXXI, 2008). Hence, the flowability powder is excellent if ( $\text{CI} \leq 10$ ), good if ( $11 < \text{CI} < 15$ ), fair if ( $16 < \text{CI} < 20$ ), passable if ( $21 < \text{CI} < 25$ ) and lastly poor if ( $\text{CI} > 25$ ).

The Hausner ratio represents the inter particle friction state. More HR is close to 1, the better is the flowability. In general, the worst flowability is observed when HR ratio is greater than 1.25 (US Pharmacopeia XXXI, 2008).

#### 2.4.6. Cold water solubility

Cold water solubility of PGS and CMPGS was determined following the method reported by Chen and Jane (1994) with minor modifications. A 100 mL of CMPGS suspension (1%, w/v) was transferred into a blender jar and blended at low speed for 3 min at 25  $^\circ\text{C}$  and stored at room temperature for 2 h. The starch suspension was then transferred to a centrifuge bottle and centrifuged at 4000 rpm for 15 min (Hettich-EBA 20 Germany), and 5 mL of the supernatant liquid was evaporated in oven (Blue M model OV-12A, USA) at 105  $^\circ\text{C}$  until a constant mass was weighed. The mass of dry residue was used to calculate the relative solubility ( $S$ ) of the sample (Eq. (11)).

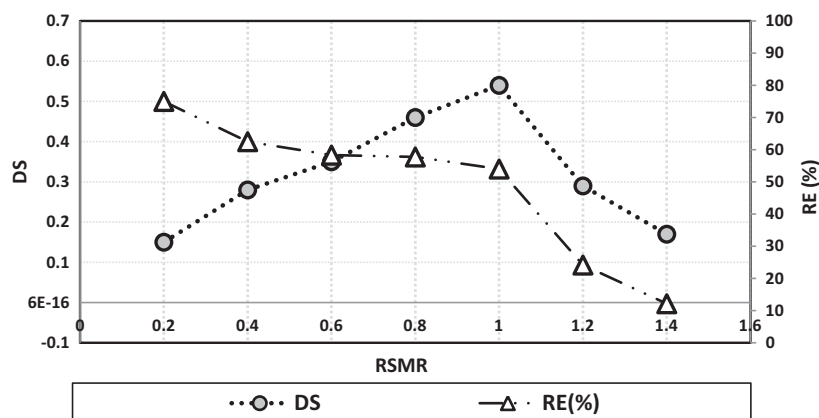
$$S (\%) = (w/w_0) \times 100 \quad (11)$$

where  $w$  refers to the solid content of the supernatant;  $w_0$  refers to the dry weight of starch sample.

### 2.5. Application of CMPGS as pharmaceutical excipient

#### 2.5.1. Tablet preparation

The formulations ( $F_1$ – $F_6$ ) were prepared only with 75% of PGS or CMPGS with different DS. The excipient powder (PGS or CMPGS) was mixed in a cube mixer to gravity



**Figure 2** Effect of the variation of RSMR on the DS and the reaction efficiency (RE).

(Giuliani) for 15 min with Ibuprofen (25%, w/w loading), as drug model by dry blending. No other component (lubricant, filler or coating agent) was added. The blended powder was then compressed into 300 mg tablets with 10 mm round shaped flat punch using single punch tablet machine (Erweka-Apparatebau, GmbH, Germany) at 50 kN. Totally 6 formulations (F<sub>1</sub>–F<sub>6</sub>) were developed and studied (Table 2).

### 2.5.2. Evaluation of tablets

The prepared tablets were evaluated for hardness value (Sotax HT1), diameter (digital caliper, Mituyoto), friability percent (Erweka), average weight (Sartorius BP 121S) and drug content uniformity according to US Pharmacopeia XXXI (2008), as shown in Table 2.

### 2.5.3. In-vitro drug release

The in vitro release studies of Ibuprofen from the prepared tablets were performed according to the US Pharmacopeia XXXI (2008), using dissolution apparatus I (Dissolution tester DT 620, Erweka). One tablet was placed in each basket and immersed in 500 mL of dissolution medium which rotated at 50 rpm and maintained at  $37 \pm 0.5$  °C. The dissolution medium was phosphate buffer of pH 6.8. Samples of 1 mL were withdrawn at specified time intervals and the volume was compensated to the initial volume by adding fresh dissolution medium after each sampling. The samples were diluted, then filtered using millipore filter (0.45 mm) and spectrophotometrically analyzed at 272 nm (Thermospectronic scientific Helios). The experiment was carried out in triplicate. The mechanism of Ibuprofen release from the prepared tablets during dissolution was determined using Korsmeyer-Peppas semi-empirical model (Korsmeyer et al., 1983):

$$M_t/M_\infty = Kt^n \quad (12)$$

where  $M_t/M_\infty$  is the fraction of drug released at time  $t$ ,  $K$  is a constant incorporating the structural and geometric characteristics of the matrix tablets,  $n$  is the release exponent, indicative of the drug release mechanism; it is the slope of log fraction drug released versus log time.

## 3. Results and discussion

### 3.1. Influence of the operational parameters on carboxymethylation

#### 3.1.1. Influence of the molar ratio (RSMR)

The influence of molar ratios of SCA to PGS on the values of DS and RE is presented in Fig. 2. The NaOH solution used in this study is 30% (w/v) and the temperature of the reaction is set at 50 °C for 1 h. The DS increased with increasing SCA/GU ratio. However, the RE decreased with the increasing of DS and RSMR. This is probably due to the competitive reaction of SCA with NaOH to form sodium glycolate (Heinze et al., 2004). The increase in RSMR reflects an increase of SCA/PGS molar ratio ( $n_{SCA}/n_{GU}$ ). Consequently, it favors this secondary reaction (Kooijman et al., 2003). When the ratio ( $n_{SCA}/n_{GU}$ ) is not more than (1.0/1.0), the concentration of SCA is reduced and all of this reagent will react with PGS. Consequently, the secondary reaction does not occur. Beyond a molar ratio of SCA/GU of (1.0/1.0), the DS decreased. Indeed, the increasing SCA/GU ratio consumes some amount

of NaOH, while, under the reaction conditions, the amount of NaOH is constant and the more the SCA is, the less the NaOH can react with GU and this leads to lower DS. The decrease of the reaction efficiency (RE) with the increase of DS, may also be the fact that SCA has a difficulty to react with the hydroxyl groups present on the chain of PGS because of the steric effects (Sangseethong et al., 2005) or the electrostatic repulsion caused by the carboxylic groups already substituted on PGS backbone (Suriyatem and Kittipongpatana, 2010).

#### 3.1.2. Influence of reaction time

Fig. 3 illustrates the effect of reaction time on DS and RE for a concentration of NaOH equal to 30% (w/v). The reaction is carried out at a temperature of 50 °C with a RSMR equal to 1.0. The reaction achieves an RE of 54% for an optimal DS equal to 0.54 over 1 h. The DS increases with the reaction time. This increase is the result of a better contact time of the etherification reagent (SCA) with PGS macromolecules. It is also reasonable that the reaction time increases the homogeneity, reinforces the swelling of PGS granules and ultimately enhances the effect of the reagents (Khalil et al., 1990). However, no further increase was observed in the DS after 1 h of reaction. The DS reached almost constant values with longer reaction times. This could be due to the equilibrium state achieved after 1 h of the reaction. This result is also similar to those found by Stojanovic et al. (2000).

#### 3.1.3. Influence of reaction temperature

The results of the influence of reaction temperature on the DS and RE are illustrated in Fig. 4. The concentration of NaOH solution is 30% and the reaction is carried with a RSMR equal to 1.0 for 1 h. The temperature for the carboxymethylation process was ranged from 20 to 70 °C.

The DS values increase with the increase of temperature of etherification approaching its maximum point at 50 °C. An increase in temperature increases the solubility of etherification agents and it also increases both the swelling of PGS and diffusion of other reagent molecules present in the reaction medium (Stojanovic et al., 2000). It is also responsible for the increase in activation energy of the reaction, and consequently the reaction rate and the DS. The maximum achieved values of DS and RE were 0.55 and 55%, respectively.

Higher temperatures (>60 °C) induced gelation of PGS and, consequently the agitation becomes difficult, and the product becomes gelatinous (Oosten, 1984). Thus, The DS values and RE remain almost constant and equal to 0.55 and 55% respectively when the temperature rises above 50 °C. It should be specified that in the case of PGS, the gelatinization temperature is in the range of 79–81 °C, but this temperature is subject to a reduction by the presence of solvent with high electron polarizability and ions, which reduce the gelatinization temperature (Oosten, 1984). In the present study, isopropyl alcohol as a solvent and the chloride ions tend to reduce the gelatinization temperature of PGS.

Contrast to other types of starch previously studied (Fang et al., 2002; Nor Nadiyah et al., 2010), at temperature above 60 °C, the effect of gelatinization started to be noticed. The product was in agglomerate but the affinity of PGS to water allows a complete starch gelatinization. Thus, the PGS molecules do not tend to bind to each other to form big agglomerates. The amount of water required in the carboxymethylation

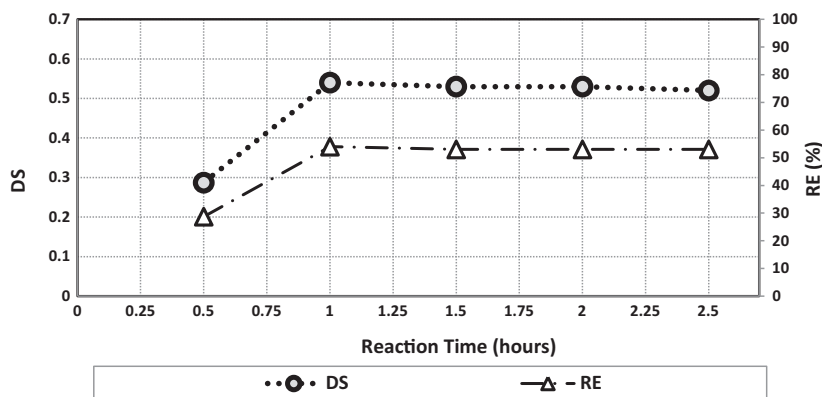


Figure 3 Variation of the DS and the RE as a function of reaction time.

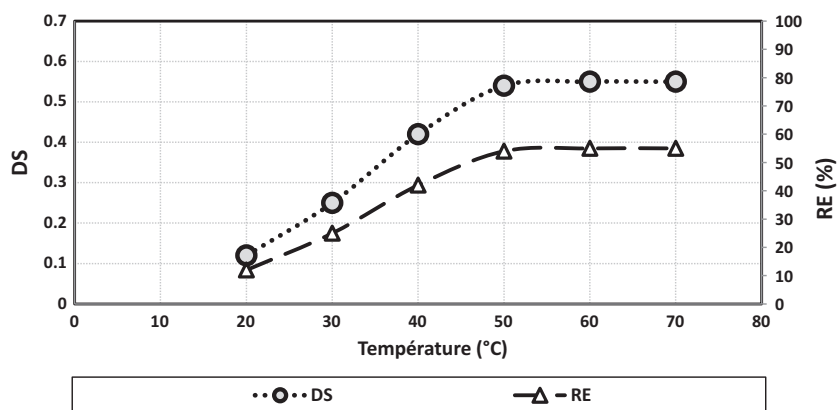


Figure 4 Variation of the DS and the RE as a function of temperature.

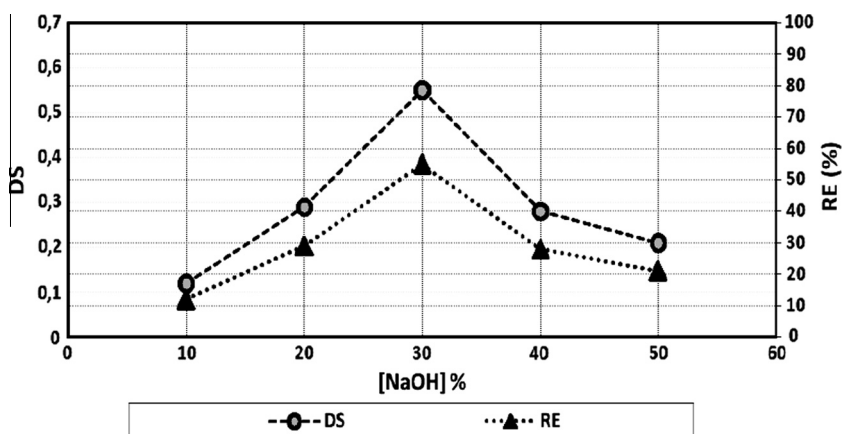


Figure 5 Effect of the concentration of NaOH on the DS and the RE.

process was sufficient. Hence, there is no loss in product recovery and no difficulty in drying process. This led to almost constant DS and RE values.

#### 3.1.4. Effect of NaOH concentration

The effect of NaOH concentration on the DS and RE of CMPGS is shown in Fig. 5. The carboxymethylation process was carried out at different concentrations of NaOH ranging from 10% to 50% (w/v). The RSMR is constant and equal to 1.0, at 50 °C during 1 h.

The DS value was found to increase significantly when the concentration of NaOH increased to 30% (w/v). The maximum degree of substitution was 0.55 with a reaction efficiency of 55%. During the process, aqueous NaOH was used to activate the reaction (Eq. (1)). The hydroxyl groups of the PGS macromolecules (GU-OH) are converted into alkoxide forms (GU-O<sup>-</sup>Na<sup>+</sup>) which then react with SCA resulting in the form of GU-O-CH<sub>2</sub>-COO<sup>-</sup>Na<sup>+</sup> (Eq. (2)) (Sangseethong et al., 2005). Treatment with NaOH at a higher concentration increases the swelling of the starch granules and produces more

(GU-O-Na<sup>+</sup>), resulting in greater opportunities for carboxymethylation to take place with the hydroxyl groups present in the PGS molecules (Stojanovic et al., 2000). The obtained DS values ranged from 0.19 to 0.55. Similar results were obtained for the DS values for some chemical modifications of starches, such as carboxymethylation of rice starch ( $0.24 < DS < 0.40$ ) (Kittipongpatana et al., 2006), cross-linked rice starch ( $0.30 < DS < 0.38$ ) (Suriyatem and Kittipongpatana, 2010), Chinese yam starch ( $0.05 < DS < 0.45$ ) (Yanli et al., 2009) and corn starch ( $0.3 < DS < 0.5$ ) (Bhattacharyya et al., 1995; Lee et al., 2010). Zhou et al. (2007) have found that the value of DS increases with the concentration of NaOH when the molar ratio between SCA and starch is constant. However, the concentration of NaOH has no effect on the DS value of carboxymethyl starch when the concentration of NaOH is two times greater than that of SCA.

Further increase in NaOH concentration was accompanied by lowering of DS values. Indeed, when the concentration of NaOH reached 40%, the DS decreases. This result can be attributed to the fact that during the process, the side reaction of NaOH with SCA (Eq. (3)) became more significant and competed with the main reaction (Eq. (2)). Similar results were also reported in previous studies on corn starch, amaranth starch, cassava starch, potato starch, pea starch and Chinese yam starch (Bhattacharyya et al., 1995; Ragheb et al., 1997; Tijssen et al., 2001b; Sangseethong et al., 2005; Yanli et al., 2009).

### 3.2. Characterization of carboxymethyl pregelatinized starch (CMPGS)

#### 3.2.1. Fourier transform infrared (FTIR)

The substitution of carboxymethyl groups on PGS molecules may be revealed by FTIR spectroscopy. Substitution was confirmed by the presence of carbonyl groups in the IR spectrum. The FTIR spectra of PGS and CMPGS are shown in Fig. 6. PGS has corresponding bands at  $3433\text{ cm}^{-1}$  due to O-H stretching vibration (Fig. 6a). The absorption band at  $2923\text{ cm}^{-1}$  shows the C-H stretching. The -CH<sub>2</sub> symmetrical band is found at  $1380\text{ cm}^{-1}$ . Weak absorption at  $1643\text{ cm}^{-1}$  for PGS, probably features the tightly bound water molecules present in PGS molecules. The absorption bands in the range of  $1300\text{--}860\text{ cm}^{-1}$  are characteristics of C-O stretching in C-O-C and C-O-H in the glycosidic molecule of PGS (Zhou et al., 2007).

Also, the FTIR spectra of CMPGS samples (Fig. 6b) show the typical absorption of PGS backbone as well as the additional peaks. New peaks occurred corresponding to specific groups after etherification reaction indicating the substitution of carboxylic groups on the PGS chains. The absorption bands are identified as the symmetrical carboxylic groups at  $1417\text{ cm}^{-1}$  and asymmetric ones at  $1603\text{ cm}^{-1}$  (Kittipongpatana et al., 2006; Lawal et al., 2008). The absorption band of O-H stretching is reduced in intensity and has shifted to  $3456\text{ cm}^{-1}$ . This could be due to the interaction of O-H group with the carboxylic group. The reduction in intensity of this band may also correspond to partly substituted O-H group with carboxymethyl group during the reaction (Fang et al., 2002).

#### 3.2.2. Grain morphology

The shape and surface structure of PGS and modified PGS granules were studied using scanning electron microscope. The SEM micrograph of PGS (Fig. 7a) at 500× magnification ( $50\text{ }\mu\text{m}$  size bar) shows a continuous phase in which enclosed air bubbles occupy a large part of the volume. The appearance of the product is due to the treatment that it underwent during gelatinization. The granular round shape has completely disappeared compared to the corn starch before gelatinization. These observations are in accord with the literature data (Colonna et al., 1984; Arthur and Kibbe, 2000; Anastasiades et al., 2002).

The SEM micrographs of CMPGS (Fig. 7b–f) show intact granules compared to the PGS. It clearly appears that the morphology of the grains obtained after the carboxymethylation reaction is directly related to DS and therefore to the type of treatment undergone by the PGS. Granules of CMPGS with DS of 0.12, 0.29 and 0.55 reacted with 10 to 30% of NaOH have smooth appearance (Fig. 7b–d), while the granules of CMPGS with DS of 0.28 reacted with 40% of NaOH present a rough surface and collapse (Fig. 7e). Granules of CMPGS with DS of 0.21 treated with a concentration of 50% of NaOH present some forms of particle agglomeration, and the sample has a similar appearance to a gel (Fig. 7f). Thus, we can conclude that an increase in the concentration of NaOH has damaged the surface of the modified starch grains. The alkaline solution probably reduces the rigidity and stability of the molecular organization of the starch granules resulting in a loss of their granular structure (Wang and Wang, 2004). Cardoso et al. (2007) reported that rice starch treatment with NaOH concentration above 24% (w/v) resulted in a

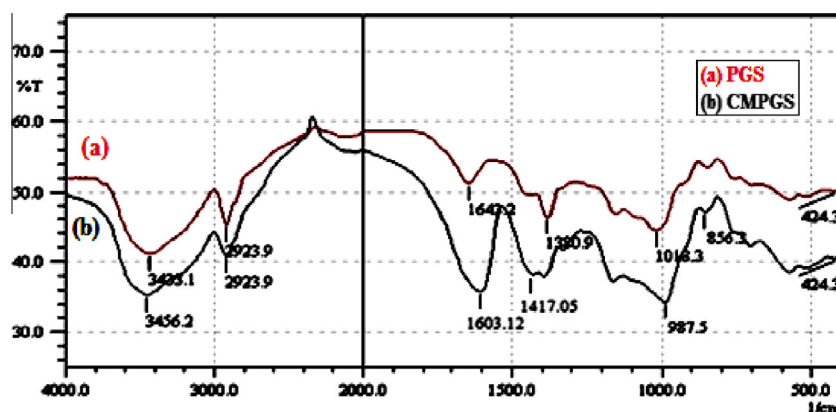
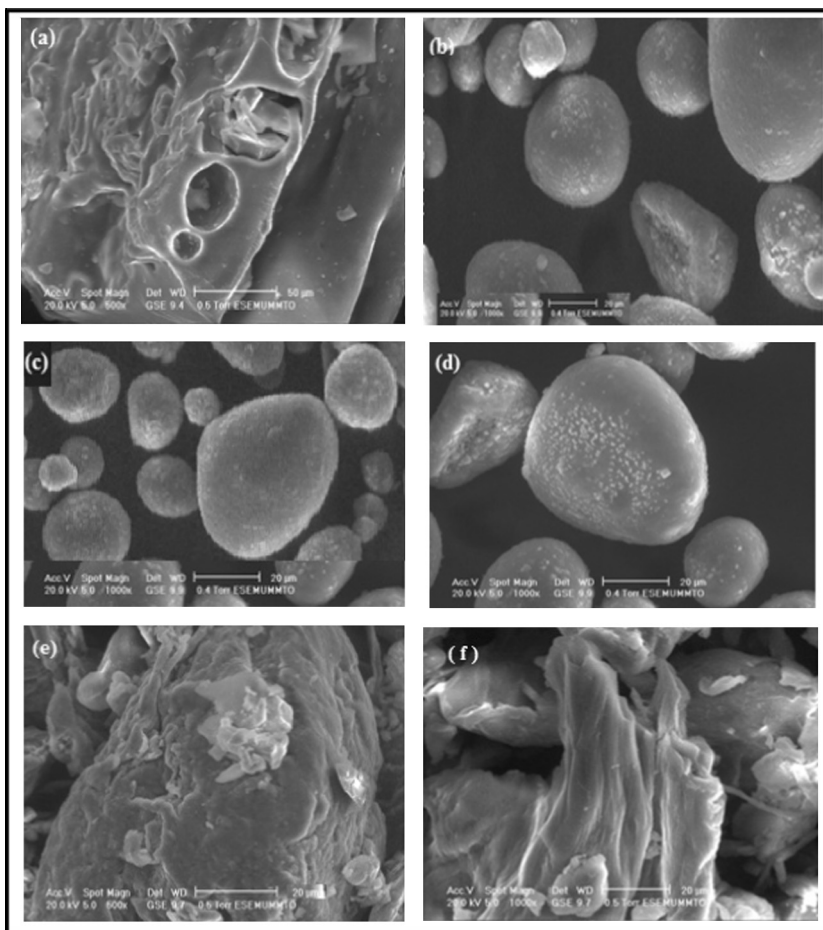
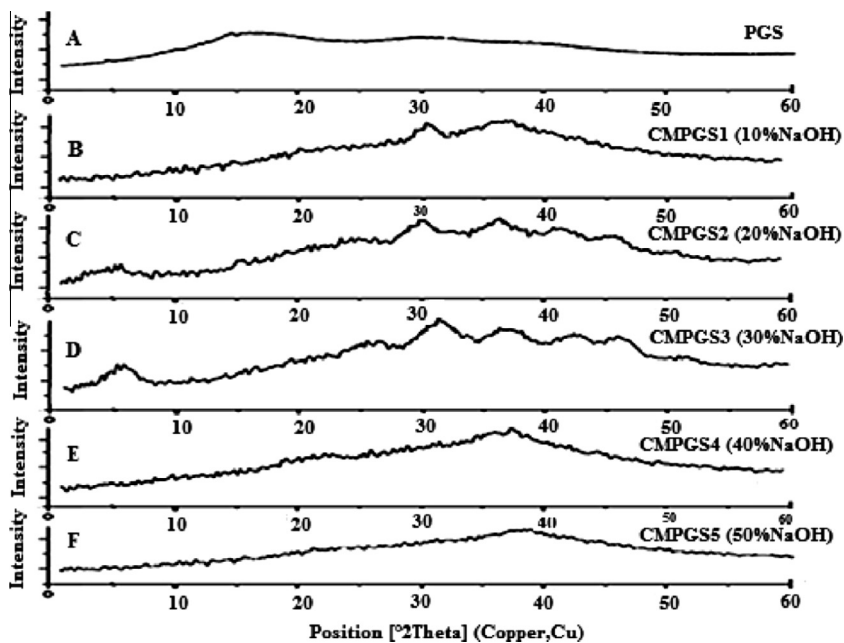


Figure 6 FTIR spectra of PGS and CMPGS.



**Figure 7** SEM photographs of PGS and CMPGS with different DS values: (a) PGS, (b) CMPGS1 (DS 0.12, 10%NaOH), (c) CMPGS2 (DS 0.29, 20%NaOH), (d) CMPGS3 (DS 0.55, 30%NaOH), (e) CMPGS4 (DS 0.28, 40%NaOH), and (f) CMPGS5 (DS 0.21, 50%NaOH).



**Figure 8** XRD profiles of PGS and CMPGS with different DS values.



progressive loss of granular morphology, probably due to a phenomenon of alkaline gelatinization. This result is also similar to those found with cassava carboxymethyl starch (Sangseethong et al., 2005). The alkalizing is the main process responsible for the change in granule morphology and loss of crystallinity (Cardoso et al., 2007). But at the same time, alkalizing allows to the agents of etherification a greater access to the starch macromolecules during the process of carboxymethylation (Lawal et al., 2008).

### 3.2.3. X-ray powder diffraction

The pregelatinized starch is a native corn starch in which the crystalline structure was changed to a V-type structure to make it partially or completely soluble in water (Ratnayake et al., 2008). The diffraction patterns of PGS reported intense peaks at 15.3°, 17.2°, 18.3° and 23.5° (Fig. 8a). Crystalline regions inside PGS adopt a polymorphic form corresponding to the V-type structure, based on left-handed single-stranded helices close-packed orthorhombicly (Zobel, 1988). V-type structure shows generally an increase in the gelatinization temperatures, better dispersibility, lesser swelling, and higher solubility in water versus A and B types (Zobel, 1988; Daniel et al., 2007).

The diffraction patterns of CMPGS indicated intense peaks at 30.1°, 36.2°, 42.2° and 46.5° (Fig. 8b–f). The tops of the diffraction spectra of CMPGS decrease with the increase in concentration of NaOH. This means that the crystallinity of the samples is greatly reduced when the concentration of NaOH increases during the carboxymethylation reaction. These results suggest that the loss of crystallinity is due to the breakdown of starch granules (Fig. 7f). The obtained results are in agreement with previous works realized on carboxymethyl Chinese yam starch (Sangseethong et al., 2005; Yanli et al., 2009). Cardoso et al. (2007) studied the effect of alkaline concentration on the gelatinization of rice starch. They reported that the crystallinity of the rice starch decreased and a loss of granule morphology was observed with the increase of NaOH concentration. Furthermore, in our study, the diffraction pattern of CMPGS has virtually disappeared at concentrations above 40% of NaOH (Fig. 8f). This result suggested that the alkaline conditions, concurrently with heat treatment caused the rupture of starch granules and the breakage of chemical bonds in starch molecules resulting in the loss of crystallinity (Chen and Jane, 1994).

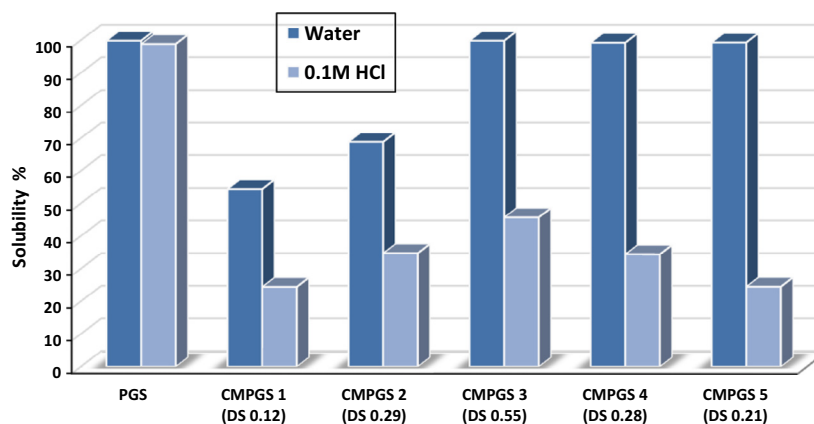
### 3.2.4. Cold water solubility

The solubility behavior in an aqueous system was investigated to study the nature of associative bonding forces within the granules. The results revealed that the solubility of CMPGS increased with the increase in DS (Fig. 9). This is due to the higher hydrophilicity of the carboxyl group which takes up more of water, resulting in maximum water solubility (Wurzburg, 1986). It seemed that an increase in cold water solubility was not only due to the introduction of negatively charged carboxymethyl groups, but also resulted from the alkalization treatment (Chen and Jane, 1994). The obtained results showed also that the strong alkaline conditions in such treatment transformed hydroxyl groups of the starch molecules into alkoxide groups. The repulsion between negative charges resulted in swelling of the starch granules and exerted a tension on adjacent crystallites of starch molecules. The modified starch granules became weaker and more soluble in cold water (Chen and Jane, 1994). The significant decrease of the solubility of CMPGS when placed into 0.1 M HCl can be related to the protonation and it reflects the non-dissociation of carboxylic acid groups (Heinze and Koschella, 2005).

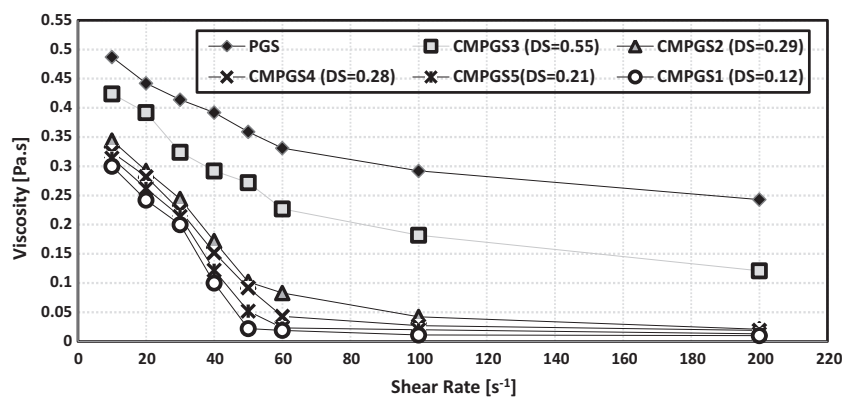
### 3.2.5. Evaluation of the rheological properties

The study of flow properties is important for evaluating the effects of operating parameters on the properties of final product especially in the pharmaceutical industry. In this study, the viscosities of PGS and CMPGS with different DS solutions in a broad range of shear rates were determined (Fig. 10). PGS has a characteristic of shear thinning behavior where the viscosity decreases along with the shear rate increasing. CMPGS samples presented lower viscosities than that of PGS at the same shear rate. The obtained profiles show a shear thinning behavior for all the studied samples.

Moreover, the viscosity of CMPGS increases with an increase in the DS. The results demonstrated that the incorporation of carboxymethyl groups in the PGS molecules improved the viscosity of PGS paste. The improvement of viscosity in CMPGS might be due to the presence of negative charges in their molecules. It is well established that the viscosity of polysaccharides is a function of their molecular sizes. So, the same molecular weight can show different viscosities if molecules had different shapes or charges. Molecules which give a greater viscosity are those which require more volume



**Figure 9** Solubility (%) of PGS and CMPGS with different DS values in water and HCl 0.1 M.



**Figure 10** Apparent viscosity of PGS and CMPGS1 (DS 0.12), CMPGS2 (DS 0.29), CMPGS3 (DS 0.55), CMPGS4 (DS 0.28), and CMPGS5 (DS 0.21).

**Table 1** Powder properties of CMPGS.

Powder	DS	$\rho_B$ (g/cm <sup>3</sup> )	$\rho_T$ (g/cm <sup>3</sup> )	CI (%)	HR	Flow character
PGS	–	0.75 ± 0.09	0.83 ± 0.04	9.63 ± 0.42	1.11 ± 0.09	Excellent
CMPGS1	0.12	0.64 ± 0.07	0.75 ± 0.08	14.66 ± 1.26	1.17 ± 0.05	Good
CMPGS2	0.29	0.68 ± 0.05	0.80 ± 0.06	15.00 ± 1.35	1.17 ± 0.10	Good
CMPGS 3	0.55	0.70 ± 0.06	0.81 ± 0.07	13.5 ± 1.26	1.15 ± 0.09	Good
CMPGS 4	0.28	0.72 ± 0.07	0.85 ± 0.09	15.29 ± 1.05	1.18 ± 0.07	Good
CMPGS 5	0.21	0.73 ± 0.09	0.86 ± 0.101	15.11 ± 1.08	1.17 ± 0.02	Good

**Table 2** Physiochemical parameters of tablets.

Formulae code	Formulae base	Average weight (mg)	Hardness (kg/cm <sup>2</sup> )	Friability (%)	Diameter (mm)	Drug content (%)
F <sub>1</sub>	CMPGS 1	301 ± 0.22	5.86 ± 0.34	0.76 ± 0.15	10.03 ± 0.06	24.97 ± 0.31
F <sub>2</sub>	CMPGS 2	299 ± 0.23	5.34 ± 0.21	0.73 ± 0.18	9.98 ± 0.03	25.10 ± 0.26
F <sub>3</sub>	CMPGS 3	300 ± 0.53	5.36 ± 0.28	0.73 ± 0.24	10.02 ± 0.05	24.99 ± 0.27
F <sub>4</sub>	CMPGS 4	299 ± 0.17	5.56 ± 0.36	0.69 ± 0.35	9.97 ± 0.08	25.28 ± 0.41
F <sub>5</sub>	CMPGS 5	299 ± 0.21	5.83 ± 0.27	0.72 ± 0.21	10.01 ± 0.07	25.24 ± 0.06
F <sub>6</sub>	PGS	302 ± 0.24	4.71 ± 0.21	0.87 ± 0.11	10.08 ± 0.04	24.98 ± 0.22

to move, leading to a greater strength to the flow (Whistler and Daniel, 1985). The increase in DS makes CMPGS molecules in more extended state as a result of the repulsion of negatively charged carboxymethyl groups and exhibited higher viscosity. At low DS values, the unsubstituted PGS is predominant. As the DS increases, the proportion of carboxymethyl functional groups increases, resulting in an increase in viscosity (Clasen and Kulicke, 2001).

### 3.3. Analysis of powder properties

The flowability results and density values of PGS and CMPGS with different DS values were studied by determining bulk density, tapped density, Carr's index (CI) and Hausner's ratio (HR). The averages of three reading values were computed (Table 1). The results of the measures of CI and HR of PGS indicated that the powder has an excellent flow character (CI = (9.63 ± 0.42)%, HR = 1.11 ± 0.09). The bulk and tapped densities of CMPGS have varied in comparison with those of PGS. This indicates that during the chemical treatment of PGS, the structure of the powder bed was changed

and the inter-granular volume reorganized. The density of CMPGS increases with the increase in DS. The results of bulk density and tapped density (g/cm<sup>3</sup>) of CMPGS were ranged from (0.64 ± 0.07) to (0.73 ± 0.09) and from (0.75 ± 0.08) to (0.86 ± 0.101) respectively. The CI (%) ranged from (13.5 ± 1.26) to (15.29 ± 1.05) indicating that the CMPGS powders have a good flow character and can be compressible without any addition of other ingredients. The Hausner's ratio ranged from (1.15 ± 0.09) to (1.18 ± 0.07). These results indicate that CMPGS has good cohesion properties. The better flow character has been obtained for CMPGS 3 with a DS value of 0.55 (CI = 13.5 ± 1.26% and HR = 1.15 ± 0.09). The overall results confirm that CMPGS is freely flowable and easily compressible. Lastly, all obtained CMPGS samples presented fairly high and typical density values compared to standard common excipients (Rowe et al., 2006).

### 3.4. Characterization of tablets

The physical properties of Ibuprofen tablets are shown in Table 2. The tablets formulae showed acceptable physical prop-

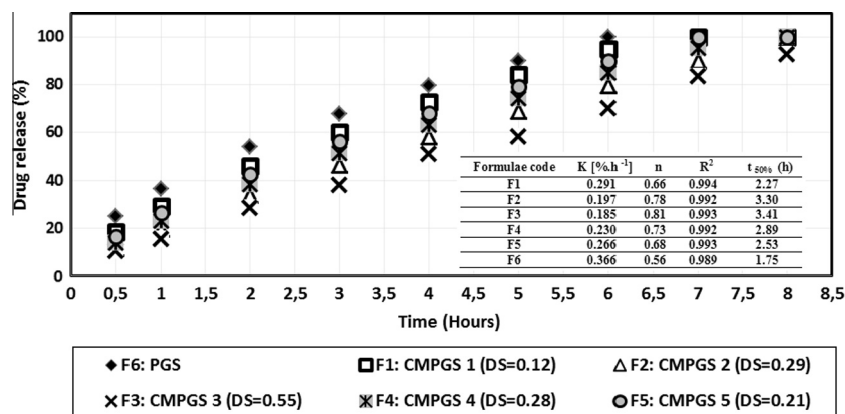


Figure 11 Dissolution profiles of tablet formulations (F<sub>1</sub>–F<sub>6</sub>).

erties. The drug content of the prepared tablets was within the requirements of *US Pharmacopeia XXXI* (2008) and no significant differences in compression properties were found. However, PGS tablets showed higher friability ( $0.87 \pm 0.11\%$ ), and less hardness ( $4.71 \pm 0.2 \text{ kg/cm}^2$ ) compared to CMPGS tablets, because insufficient hardness resulted in high friability. Even so, the results always remain within the limits of *US Pharmacopeia XXXI* (2008). CMPGS generated particles with improved compression when compared to the PGS tablets. These results suggest that these compounds may be used as excellent excipients for tablet dosage forms.

The release of Ibuprofen from the prepared tablets was studied using phosphate buffer of pH 6.8 as dissolution media. The tested polymers did not interfere with the analysis of Ibuprofen in the drug release studies because there were no significant peaks for the used polymers observed in the UV range from 200 to 400 nm using phosphate buffer of pH 6.8 as blank.

The release profiles of Ibuprofen from F<sub>6</sub> tablets, based on PGS, showed that 100% of the drug was released after 6 h in phosphate buffer of pH 6.8, while 50% of the drug was released after 1.75 h as shown in Fig. 11. In fact a rapid and significant loss of gel-layer integrity was observed for the PGS tablets in dissolution media. These results may be due to that, Ibuprofen is a weak acidic drug ( $pK_a = 4.41$ ) and its solubility is pH dependent which increases rapidly at pH values higher than the drug  $pK_a$  value. The solubility of the drug was previously determined by *Watkinson et al.* (1993) and was found to be 0.52 and 3.70 mg/mL in (pH 6.0) and (pH 7.0), respectively. However, some studies have reported that pregelatinized starches may also have sustained release properties (*Nakano et al.*, 1987). *Herman and Remon* (1989) have investigated the effect of many parameters on the sustained release properties of pregelatinized starch and have found that the ratio amylose/amylopectin is the most important factor influencing swelling characteristics and in vitro drug release rate. Tablets based on pregelatinized starch (25% amylose w/w) are divided into several pieces, increasing the contact surface with the dissolution medium and leading to faster drug release. While pregelatinized high amylose starch (70% of amylose) does not form a coherent gel layer and does not sustain release, but pregelatinized waxy corn starch (100% of amylopectin w/w and amylose free) was reported to form a gel layer during hydration and to decrease the drug release rate. Anyway, the obtained swollen gel layer was reported to be very weak and

the tablet erosion may considerably accelerate the drug release (*Herman and Remon*, 1989). The in vitro cumulative drug release profile of CMPGS formulations (F<sub>1</sub>–F<sub>5</sub>) showed percentages ranging from 92.69% to 100%. Among these five formulations, F<sub>1</sub> showed the highest percentage of drug release after 6 h, compared to F<sub>3</sub> which showed sustained drug release. During this study it was observed that the tablets were initially swell and no erodible over the test period. The drug release pattern of tablets varied according to DS of CMPGS. In F<sub>1</sub> formulation (CMPGS 1, DS = 0.12), 100% of the drug is released at 2.27 h and 50% of the total loaded drug released at 2.27 h. Whereas in the case of F<sub>2</sub> formulation, (CMPGS 2, DS = 0.29), tablets form a gel matrix and hence retard the drug release. Indeed, this formulation (F<sub>2</sub>) released 99.7% of the active ingredient after 8 h with a half of the active ingredient released after 3.30 h. Further, the increase in DS of CMPGS used in formulation retards the drug release but all formulations released the drug gradually up to 92% beyond 8 h. This may be attributed to the increased swelling of polymers with higher DS value. The overall data on the in vitro dissolution studies closely indicate that among the six formulations, F<sub>3</sub> (CMPGS 3, DS = 0.55) was found to be the best in terms of sustained release of the active ingredient. Indeed in this formulation, 15.5% of the drug released at the first hour, 50% of the total loaded drug released at 3.41 h and 92.69% of loaded drug released after 8 h.

According to the achieved results, it clearly appears that by increasing the DS of CMPGS used in different formulations, the drug release rate from the tablets was found to be decreased. This may be due to the increased hydration or swelling characteristics of polymers with increased DS. The swelling capacity of substituted polymers by ionic groups

Table 3 Linear correlation coefficient,  $R^2$ , and  $n$  values for the release of Ibuprofen from tablets according to Korsmeyer-Peppas semi-empirical model.

Formulae code	K (% h <sup>-1</sup> )	n	R <sup>2</sup>	t <sub>50%</sub> (h)
F <sub>1</sub>	0.291	0.66	0.994	2.27
F <sub>2</sub>	0.197	0.78	0.992	3.30
F <sub>3</sub>	0.185	0.81	0.993	3.41
F <sub>4</sub>	0.230	0.73	0.992	2.89
F <sub>5</sub>	0.266	0.68	0.993	2.53
F <sub>6</sub>	0.366	0.56	0.989	1.75

depends on the pH and ionic strength of the surrounding medium (Mulhbacher et al., 2006). Indeed, in a medium at pH values above the  $pK_a$  of the CMPGS ( $pK_a$  of about 4.2), the carboxymethyl groups (CM) are deprotonated. The gel formed around the tablet upon contact with the dissolution medium being deprotonated, enhances hydration of CMPGS matrix by increasing the repulsive forces between the groups ( $COO^-$ ), which increase with the increase of DS. This hydration of CMPGS allows gradual release (Sangseethong et al., 2005).

In-vitro drug release data of formulations  $F_1$  to  $F_6$  were fitted to Korsmeyer-Peppas equation to ascertain the pattern of drug release (Table 3). The  $R^2$  was evaluated for all the formulations ( $F_1$ – $F_6$ ) and its value was close to 0.98. According to Korsmeyer-Peppas equation, the release exponent “ $n$ ” value is greater than 0.5, which indicates that the mechanism of drug release for all formulations is non-Fickian diffusion type. For the tablets, when  $n < 0.45$ , the drug release is controlled by diffusion and when  $n > 0.98$ , the drug release is controlled by the matrix erosion. Values of  $n$  between 0.45 and 0.98 indicate a superposition of both phenomena. In tablets formulation based on CMPGS ( $F_1$ – $F_5$ ), the mean  $n$  values obtained were ranged between 0.66 ( $R^2 = 0.989$ ) and 0.81 ( $R^2 = 0.993$ ), which suggested that the drug release was controlled by the superposition of the diffusion and erosion (Korsmeyer et al., 1983; Peppas, 1985). This indicates that the drug was diffusing through the tablet at the same time as polymer relaxation was taking place. On contact with dissolution medium, a hydrophilic matrix based on CMPGS increases in size due to the entry of the solvent and allows the polymer to swell up forming a barrier to drug release. The drug particles would then move through this gel layer allowing drug to be released (Colombo et al., 2000). It was found that the polymer networks showed controlled release of drug thus slowing down the diffusion rate of the drug molecule through the matrices (Conti et al., 2007; Liu et al., 2005; Maderuelo et al., 2011). It has been shown that the DS is one of the major factors determining the properties of drug delivery (Mulhbacher et al., 2001, 2004; Calinescu et al., 2005, 2007).

#### 4. Conclusion

In this study, the optimization of the carboxymethylation reaction conditions of pregelatinized corn starch has been successfully carried out. The optimum conditions to obtain CMPGS with high DS (0.55) and reasonable RE (55%) were found to be at a 30% (w/v) concentration of aqueous NaOH with a molar ratio of SCA to GU of 1.0:1.0 during 1 h at 50 °C. Increasing a molar ratio of SCA to GU resulted in increasing DS but at a molar ratio upper to 1.0:1.0, a decrease in DS and RE was noted. NaOH was found to be an important factor in increasing the DS and RE. Increasing concentration of aqueous NaOH increased the DS and RE but only to a certain extent. Higher concentration of NaOH caused a decrease in both of these values. The SEM photographs indicated that alkali treatment was responsible for the change of the granular surface and structure of the modified starch. The diffraction patterns of CMPGS have indicated intense peaks that have virtually disappeared at concentrations above 40% of NaOH. Properties of CMPGS with various DS were also determined. It was found that all CMPGS samples were completely soluble

in cold water and less soluble in acid medium. The viscosity increased with increasing DS.

Tablets were prepared by direct compression using modified PGS with different DS and Ibuprofen as model drug. The DS variation of CMPGS allows varying release profiles. So, increasing DS value of CMPGS decreased the drug release from the tablets. The release patterns showed a sustained release following the Korsmeyer-Peppas kinetic model. The drug release mechanism of these monolithic matrix systems is non-Fickian diffusion.

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