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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 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

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insoluble in cold water and consists of granules whose size, composition, physiochemical 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 (Podczeck, 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 physiochemical 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 (García 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 alkalinization of GU–OH group within the PGS molecule are activated and converted into a more reactive alkaline form (GU–O^-.):

$$GU\text{–}OH + NaOH \rightarrow GU\text{–}O^-Na^+ + H_2O \quad (1)$$

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

$$GU\text{–}O^-Na^+ + ClCH_2COO^-Na^+ \rightarrow GU\text{–}O\text{–}CH_2COO^-Na^+ + NaCl \quad (2)$$

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

$$ClCH_2COONa + NaOHOH \rightarrow OHCH_2COO^-Na^+ + NaCl \quad (3)$$

$$ClCH_2COONa + OH\text{–}CH_2COO^-Na^+ \rightarrow (NaOOCCH2)_2O + HCl \quad (4)$$

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 starchs 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; Tijsen 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 starchs. 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.