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Blends of cross-linked high amylose starch/pectin loaded with diclofenac

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ABSTRACT

Polymers blends represent an important approach to obtain materials with modulated properties to reach different and desired properties in designing drug delivery systems in order to fulfill therapeutic needs. The aim of this work was to evaluate the influence of drug loading and polymer ratio on the physicochemical properties of microparticles of cross-linked high amylose starch–pectin blends loaded with diclofenac for further application in controlled drug delivery systems. Thermal analysis and X-ray diffractograms evidenced the occurrence of drug–polymer interactions and the former pointed also to an increase in thermal stability due to drug loading. The rheological properties demonstrated that drug loading resulted in formation of weaker gels while the increase of pectin ratio contributes to origin stronger structures.

1. Introduction

Drug delivery is a broad field of research in the pharmaceutical sciences, for which the development of novel materials suitable to aid in controlling the drug release according to therapeutic needs plays an important role. In this sense, blends of already known polymers represent a rational approach to obtain materials with different and modulated properties that enable their use for specific goals (Carbinatto, Castro, Cury, Magalhães, & Evangelista, 2012; Ebube & Jones, 2004; Lecomte, Siepmann, Walther, MacRae, & Bodmeier, 2005; Patel & Patel, 2007; Prezotti, Meneguin, Evangelista, & Cury, 2012; Wang, Hu, Du, & Kennedy, 2010). This approach can be advantageous, since apart from working with well known substances, it avoids the high cost of synthesizing new materials. Additionally, the changes in polymer ratio can result in a wide range of physicochemical properties that should provide different drug delivery patterns (Lecomte et al., 2005). Starch is one of the most abundant available polymers and can be obtained from a variety of sources. It is constituted by amylose, representing the linear fraction of the macromolecule, while amylopectin is the highly branched fraction. High amylose, a modified starch containing 70% of amylose, has been reported as possessing improved properties for controlled drug delivery purposes in relation to conventional starch (Onofre, Wanga, & Mauromoustkos, 2009; Rioux, Ispas-Szabo, Aït-Kadi, Mateescu, & Juhász, 2002). Moreover, chemical reactions (esterification, etherification, oxidation) of hydroxyl groups of high amylose starch can be useful to modulate some of its characteristics, such as solubility, swelling, rheological properties, film formation and biodegradation rate (Rioux et al., 2002).

Cross-linking has been shown to be a key technique for modifying the properties of starches and can be achieved by adding intra- and intermolecular bonds (Singh, Kaur, & McCarthy, 2007). Sodium trimetaphosphate (STMP), monosodium phosphate, sodium tripolyphosphate, epichlorohydrin, phosphoryl chloride, a mixture of adipic acid and acetic anhydride, and vinyl chloride are the main agents used to cross-link food grade starches (Wattanchant, Muhammad, Hashim, & Rahman, 2003; Woo & Seib, 1997; Yeh & Yeh, 1993). High amylose contents combined to physical and chemical modifications of this material result, for example, in products with higher viscosity and in granules that are more resistant against swelling (Richardson, Jeffcoat, & Shi, 2000; Van Hung, Maeda, & Morita, 2006).

Many researchers have demonstrated the successful use of high amylose starches cross-linked by different chemicals, such as epichlorohydrin and STMP, in the development of controlled drug delivery systems (Cury, Castro, Klein, & Evangelista, 2009a; Cury, Castro, Klein, & Evangelista, 2009b; Fang et al., 2008; Lenaerts, Dumoulin, & Mateescu, 1991; Li et al., 2009; O'Brien, Wang, Vervaet, & Remon, 2009).

Pectins are a family of complex polysaccharides constituted mainly of linearly connected α-(1-4)-D-galacturonic acid residues partially esterified with methanol. The degree of methoxylation

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(DM) is used to classify pectins as high methoxyl pectins (DM > 50) and low methoxyl pectins (DM < 50) (Ghaffari, Navaee, Oskoui, Bayatil, & Rafiee-Tehrani, 2007; Lutz, Aserin, Wicker, & Garti, 2009). They are widely used in the pharmaceutical industry to compose hydrophilic matrices in oral controlled release dosage forms (Sungthongieen, Sriamornsak, Pitaksuteepong, Somsiri, & Puttipipatkhachorn, 2004; Wei, Sun, Wu, Yin, & Wu, 2006).

In this work, two polymers with different properties were blended and submitted to cross-linking process in order to prepare materials with distinct properties. The influence of drug incorporation on these properties was evaluated by incorporating diclofenac in the polymer microparticles.

2. Materials and methods

2.1. Materials

Pectin (type LM-506CS, lot: S74431) was provided by CP Kelko (Copenhagen, Denmark), high amylose starch (Hylon VII, lot: HA9140) was obtained from National Starch & Chemical (New Jersey, EUA), sodium trimetaphosphate (lot: 112K1365) was purchased from Sigma–Aldrich Co. (St. Louis, USA), sodium hydroxide (lot: 6 11648) was supplied by Grupo Química (Rio de Janeiro, Brazil), 37% hydrochloric acid (lot: 29957) was provided by Quimis (Diadema, Brazil), ethyl alcohol (lot: 127698) was obtained from Synth (Diadema, Brazil), and sodium diclofenac (lot: 061117-1) was provided by Henrifarma (São Paulo, Brazil).

2.2. Cross-linking reaction

The cross-linking reaction of polymers blends at different ratios (4:1, 1:1 and 1:4) was performed in alkaline aqueous media and STMP was used as cross-linker, based on procedure described by Carbinatto et al. (2012) with minor modifications. Briefly, the polymers blends (5%) were dispersed in pre-heated water at 80 °C by mechanical stirring until to reach room temperature. The base (4% of NaOH pellets) was then added to the dispersion and completely dissolved prior the addition of the solid cross-linker (30% of polymer mass). After the dispersion was kept under stirring for 2 h, 3 mol L^{-1} HCl (about 2%, v/v) was added in order to adjust the pH to 6 and to stop the reaction. The samples were washed once with 85% ethanol, then eight times with 65% ethanol and finally once with absolute ethanol and filtered under vacuum.

The samples were labeled according to polymers names HA–P (high amylose–pectin) followed by their respective ratios in the mixture. The physical mixtures were indicated by the prefix PM while the suffix WD and CD describe the samples without cross-linker and the samples containing diclofenac (SD), respectively.

2.3. Drug loading/effect of SD concentration on drug loading

Diclofenac was incorporated into the cross-linked samples by soaking them into drug solutions at different concentrations (3 mg/mL, 6 mg/mL, 9 mg/mL), under stirring for 30 min at room temperature. After that, the samples were frozen and dried by lyophilization overnight (−30 °C), since, according to previous tests, the oven-drying was not able to yield powdery product. The drug content and efficiency of incorporation were calculated according to Eqs. (1)–(3). The samples prepared from 9 mg/mL drug solutions were selected for this study because they led to higher efficiency of incorporation.

2.4. Determination of SD content of the microparticles

An accurately weighed mass of microparticles (about 1 g) was added to 50 mL of water and the dispersion was stirred during 48 h. The products were then centrifuged at 3500 rpm for 70 min and the SD concentration in the supernatant was quantified by UV absorption at 276 nm on spectrophotometer (Hewlett Packard, Mod. 8453). The analyses were performed in triplicate and the drug content was calculated according to the following equation.

$$\mathrm{DC}\,(\%) = \frac{A_q}{A_i} \times 100 \quad (1)$$

where DC (%) is the drug content (%); A_q is the amount of drug quantified in the sample and A_i is the initial amount of drug added to the sample.

2.5. Efficiency of incorporation

For the determination of the amount of SD entrapped into the particles, 10 mL of ethanol were added to an accurately weighed mass of drug-containing microparticles (about 1 g), stirred for 5 min and filtered. The drug alcoholic solution was evaporated at room temperature to dryness and the residue was redispersed in 25 mL of purified water. This dispersion was kept under magnetic stirring (30 min) for complete drug dissolution. The drug concentration in the supernatant was quantified by UV absorption at 276 nm on spectrophotometer (Hewlett Packard, Mod. 8453) and assumed as free drug. The tests were performed in triplicate and the efficiency of incorporation was calculated according to Eqs. (2) and (3).

$$\mathrm{FD}\,(\%) = \frac{A_q}{A_i} \times 100 \quad (2)$$

$$\mathrm{EI}\,(\%) = 100 - \mathrm{FD} \quad (3)$$

FD (%) is the free drug (%), A_q is the amount of drug quantified in the sample and A_i initial amount of drug added to the sample. EI (%) is the efficiency of incorporation.

2.6. Size and shape properties

Particle size distribution and shape of samples were analyzed with a *Motic Images Advance 3.2* image analyzer coupled to a Leica MZ APO™ stereoscope, by measuring Feret's diameters at 0° and circularity of at least 300 particles at 32-fold magnification.

2.7. Thermoanalysis

2.7.1. Thermogravimetric analysis (TG) and differential thermogravimetric analysis (DTG)

TG and DTG curves of samples SD, HA-P 4:1 WD, HA-P 4:1 CD, HA-P 1:1 WD, HA-P 1:1 CD, HA-P 1:4 WD and HA-P 1:4 CD were recorded with a TA Instruments (SDT 600) under nitrogen atmosphere at heating rate of 10 °C/min between 25 and 1200 °C for 5 mg of samples sealed in alumina pans.

2.7.2. Differential scanning calorimetry (DSC)

DSC curves of samples SD, HA-P 4:1 WD, HA-P 4:1 CD, HA-P 1:1 WD, HA-P 1:1 CD, HA-P 1:4 WD, HA-P 1:4 CD, PM HA-P 4:1 WD and PM HA-P 1:4 WD were registered in a TA Instruments DSC 2910 at heating rate of 10 °C/min between 25 and 600 °C, under nitrogen atmosphere (100 mL/min). About 5 mg of samples sealed in alumina pan was used for each measure.

2.8. X-ray diffraction

The X-ray diffraction analysis of P, HA, SD and samples HA-P 4:1 WD, HA-P 4:1 CD, HA-P 1:1 WD, HA-P 1:1 CD, HA-P 1:4 WD e HA-P 1:4 CD were performed on a X-ray diffractometer (Siemens® – Model D5000), using nickel-filtered Cu Kα radiation (tubeoperating