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.

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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 amylpectin 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, Ipsas-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 methoxyla...
(DM) is used to classify pectins as high methoxyl pectins (DM > 50) and low methoxyl pectins (DM < 50) (Ghaffari, Navaee, Oskouei, 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 (Sunthongtueen, Srimornsak, Pitaksuteepong, Somsiri, & Puttipipattakhorn, 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 amyllose starch (Hylon VII, lot: HAY140) was obtained from National Starch & Chemical (New Jersey, USA), 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 2h, 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 amyllose–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 48h. 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.

\[ DC(\%) = \frac{A_d}{A_i} \times 100 \]  

where DC (%) is the drug content (%); \( A_d \) 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).

\[ FD(\%) = \frac{A_d}{A_i} \times 100 \]  

\[ EI(\%) = 100 – FD \]  

FD (%) is the free drug (%), \( A_d \) 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
2.9. Rheological measurements

Polymers aqueous dispersions (10%) were prepared and their dynamic viscoelastic properties were measured by using a controlled stress rheometer (Haake Rheostress 1) (Gebruder Haake, Germany) equipped with cone-plate (C35/2T1) of 35 mm diameter and a gap of 105 μm. A circulating water bath (HAKE C25P) for sample temperature control and a software (Rheowin 3) for data acquisition were used. All measurements were carried out in triplicate, within the linear viscoelastic range, at 37 °C. In order to determine the linear viscoelastic region, stress sweeps between 0.1 and 100 Pa were performed, at a low frequency (1 Hz). Small deformation oscillatory experiments were conducted by using two steps of rheological measurements: (1) frequency sweeps at a constant stress (1 Pa) and angular velocity range of 0.6 to 623 rad/s to obtain mechanical spectra by recording the dynamic moduli G’ and G” and (2) creep/recovery tests were carried out at constant stress (1 Pa). In this assay the stress was applied instantly and maintained for a period of 150 s. After removing the stress, compliance was measured during further 150 s.

3. Results and discussion

3.1. Drug loading and efficiency of incorporation

The drug loading was not significantly influenced by both polymer ratio and drug concentration in solution, since all samples presenting high drug level (92–98%). However, the highest efficiency of incorporation of SD into microparticles was obtained from 9 mg/mL SD solutions, which were then selected for the preparation of samples for further analysis.

3.2. Size and shape properties

Drug incorporation led to a decreasing of particle size, since CD samples presented a highest percentage of particles in smallest size ranges, as can be seen in size distribution profiles (Fig. 1). This behavior indicates that drug incorporation resulted in a more packed network due to drug–polymer interactions. The Feret’s diameter establishes a quantitative analysis of particle size and is defined as the distance between two parallel tangents of the particle at an arbitrary angle (Boschetto & Giordano, 2012). Their average values (Table 1) confirmed the tendency of decrease of size due to the drug addition.

![Fig. 1. Size distribution of samples.](image)

Circularity is a two-dimensional geometric tolerance that controls how much a feature can deviate from a perfect circle defined by the value 1 (Jones et al., 2008). The high circularity of the samples, 0.704 and 0.756 (Table 1), and the narrow variation between the values demonstrate their shape regularity (Goyanes, Souto, & Martínez-Pacheco, 2011; Tunón, Börjesson, Frenning, & Alderborn, 2003).

<table>
<thead>
<tr>
<th>Samples</th>
<th>Diameter (μm)</th>
<th>Circularity</th>
<th>Residual mass (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HA-P 4:1 WD</td>
<td>69.16 ± 21.353</td>
<td>0.730 ± 0.0524</td>
<td>45.76</td>
</tr>
<tr>
<td>HA-P 4:1 CD</td>
<td>45.78 ± 21.387</td>
<td>0.716 ± 0.0625</td>
<td>53.74</td>
</tr>
<tr>
<td>HA-P 1:1 WD</td>
<td>61.92 ± 19.788</td>
<td>0.756 ± 0.0426</td>
<td>45.50</td>
</tr>
<tr>
<td>HA-P 1:1 CD</td>
<td>45.03 ± 20.902</td>
<td>0.704 ± 0.0552</td>
<td>47.27</td>
</tr>
<tr>
<td>HA-P 1:4 WD</td>
<td>69.41 ± 21.069</td>
<td>0.742 ± 0.0471</td>
<td>35.19</td>
</tr>
<tr>
<td>HA-P 1:4 CD</td>
<td>42.61 ± 18.558</td>
<td>0.720 ± 0.0539</td>
<td>35.52</td>
</tr>
</tbody>
</table>

3.3. Thermoanalyses

TG and DTG curves of SD (Fig. 2) show an initial peak at 65 °C, which should be related to moisture evaporation (Bartolomei, Rodomonte, Antoniella, Minelli, & Bertocchi, 2007). A second and main peak (about 30% of mass loss) occurs in three steps among 270–375 °C and it can be attributed to SD melting and decomposition (Sipos, Szűcs, Szabó, Erős, & Szabó-Révész, 2008). The TG/DTG curves of 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, HA-P 1:4 CD (Fig. 2) show a first peak around 40–110 °C attributed to moisture evaporation, as it has been reported for others polysaccharides (Einhorn-Stoll, Kunzek, & Dongowski, 2007; Godeck, Kunzek, & Kabbert, 2001; Shi & Gunasekaran, 2008). The main peak was observed between 180 and 400 °C and the relative intensity of this peak was higher for samples CD than for samples WD, suggesting the occurrence of both polymer degradation and drug melting, since these events occur in the same temperature range and probably are integrated. The CD thermograms showed a discrete shoulder between 210 and 220 °C that indicates the decomposition of more than one substance. The presence of this shoulder unchanged in the thermoanalytical profile once again suggests physicochemical interactions between drug and polymer (Mora, Longhi, & Granero, 2010).

Sample 1:4 WD (Fig. 2) shows a peak at 134 °C, which can result from loss of chemical bonded water (Shi & Gunasekaran, 2008). The presence of this event only in this sample can be attributed to the higher proportion of pectin, which is the most crystalline polymer. Another peak above 900 °C can be observed in thermogravimetric curves of samples WD, indicating that the drug incorporation promoted the increase of thermal stability, a fact that is confirmed by higher residual mass (%) of samples CD (Table 1). The drug–polymer interaction should have also improved thermal stability of SD, since its decomposition peak at 800 °C is not present in thermograms of CD samples. The overall modifications in thermal behavior of samples WD and CD should be attributed to the structural differences promoted by drug–polymer interactions.

The DSC curve of SD (Fig. 3) shows a first little endothermic event at 65 °C which must be related to the moisture evaporation and the next well defined endothermic peak around 290 °C related to drug melting (280–294 °C). The exothermic peak (300 °C) is attributed to the decomposition by oxidation reaction (Puttipipatkachorn, Pongjanyakul, & Priprem, 2005; Szűts, Budai-Szűcs, Erős, Otomo, & Szabó-Révész, 2010). The DSC curves of PM are depicted in Fig. 3, in which there are three endothermic peaks between 90 and 400 °C. The first, around 100 °C, can be related to moisture evaporation in agreement with TG/DTG achievements, while the second one, about
200 °C, should be attributed to depolymerization of pectin chains, which is confirmed by the highest intensity of this peak in the sample with the greatest pectin amount (PM HA-P 1:4) [Einhorn-Stoll et al., 2007; Shi & Gunasekaran, 2008]. The third peak above 244 °C is attributed to the high amylose starch degradation (Massicotte, Baille, & Mateescu, 2008).

The DSC curves of samples WD and CD (Fig. 3) showed similar profiles; nevertheless, samples CD showed a decrease of Tm of polymer in relation to samples WD. In addition, the endothermic and exothermic peaks of diclofenac are absent in CD samples. Both events indicate that SD is molecularly dispersed within the polymer matrix, building a solid solution (Sipos et al., 2008).

The change in the Tm of the polymer should also be attributed to morphological modifications experienced by polymer matrix, such as the size of crystallites and the crystallinity degree due to drug–polymer interactions (Devine et al., 2006).

3.4. X-ray diffraction

The diffractogram patterns of samples (SD, HA, P, 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) are exhibited in Fig. 4. The high amylose starch (HYLON VII®) diffractogram shows characteristic peaks of B structure around 17°, 19°, 23° and 25° (2θ) [Freire, Fertig, Podczeck, Veiga, & Sousa, 2009; Mishra, Datt, & Banthia, 2008]. The pectin diffractogram presents intense and well defined peaks at 12.7°, 18.42°, 25.32° and 40.14° (2θ), showing its crystalline structure (Mishra et al., 2008).

For all HA–P mixing ratios in WD microparticles, the characteristic peaks of high amylose starch and pectin are absent, behavior that can be attributed to the amorphization of samples due to the lyophilization process (Mora et al., 2010) and to the structural reorganization promoted by the cross-linking reaction. The SD diffractogram exhibits significant peaks characteristic of this drug around 15.39°, 17.42° and 27.24° (2θ) (Fini, Moyano, Ginés, Martinez-Perez, & Rabasco, 2005). The disappearance of SD peaks in CD microparticles, mainly at low values of 2θ, should be result from the destruction of the crystalline structure, which involves changes in both crystallites size and crystallinity degree (Devine et al., 2006). These morphological changes can occur due to progressive amorphization and/or dissolution of the drug inside the polymer matrix, since drug molecules interact with polymer and its original crystalline structure becomes deformed (Fini et al., 2005). The set of X-ray diffraction results reinforce the occurrence of drug–polymer interactions, as indicated by thermal analysis data.

3.5. Rheological properties

The mechanical spectra data can be used to classify the structure of gels as weak or strong (Martínez-Ruvalcaba, Chornet, & Rodriguez, 2007). The mechanical spectra of WD and CD microparticles are shown in Fig. 5, in which it can be observed that G' values remained higher than G″ values within the whole frequency range explored and the values were quasi parallel, displaying the elastic gel behavior of all materials. In addition, both samples WD and CD behaved as strong or true gel, characteristic of covalently cross-linked networks, since G′ values were nearly frequency independent (Grassi, Lapasin, Grassi, & Colombo, 2006; Martínez-Ruvalcaba et al., 2007; Rosalina & Bhattacharya, 2002; Szüts et al., 2010; Yoneya, Ishibashi, Hironaka, & Yamamoto, 2003).

The drug loading did not qualitatively affect the rheological behavior that remained as gel materials, although both the G′ values and the difference between G′ and G″ values were lower than those exhibited by samples WD, indicating that the drug addition resulted in the weakening of the polymer network (Martínez-Ruvalcaba et al., 2007; Szüts et al., 2010). This decrease of G′ values that demonstrate the less pronounced elastic properties of gels than their respective WD samples, suggests that the SD interactions with carboxyl groups of the polymers prevent
the original H bond formation between them. Similar behavior was related for PAA/PVA hydrogel containing aspirin (Mac Gann, Higginbotham, Geever, & Nugent, 2009) and protein-polysaccharide systems containing salbutamol (Saxena, Kaloti, & Bohidar, 2011). This weakening of network by drug incorporation is related to a “plasticizing effect” of the drug that disturbs macromolecular interactions of gel network (François, Rojas, Daraio, & Bernik, 2003).

The variation of storage modulus ($G'$) at low frequencies in a log–log plot of $G'$ versus $\omega$ follows the power law (Saxena et al., 2011), given by:

$$G' = S\omega^n$$

where $G'$ is the storage modulus; $S$ the gel strength; $\omega$ the oscillation frequency and $n$ is the viscoelastic exponent.

The $n$ and $S$ values have shown to be sensitive to the cross-linking density within the polymer network, allowing a quantitative estimation of strength of gel structures (Nyström, Walderhaug, Hansen, & Lindman, 1995; Scalan & Winter, 1991; Watase, Nishinari, & Clark, 1989). In this sense, the decrease of distance is represented by higher $S$ values and an increase of the cross-linking density, both events related to stronger gel structures. Inversely, the decrease of $n$ exponent values with increasing of cross-linking density was reported in a study with PVA gels (Morris, Rees, Thom, & Welsh, 1977).

Analogously, samples WD built stronger gels, according to their low values of $n$ and highest values of $S$ (Table 2), while samples CD should result in a looser and weaker structure. Besides, the

<table>
<thead>
<tr>
<th>Samples</th>
<th>$G'$ (Pa)</th>
<th>$%R$</th>
<th>$n$</th>
<th>$S$</th>
</tr>
</thead>
<tbody>
<tr>
<td>HA-P 4:1 WD</td>
<td>105.21</td>
<td>48.15</td>
<td>0.058</td>
<td>92.94</td>
</tr>
<tr>
<td>HA-P 4:1 CD</td>
<td>9.67</td>
<td>11.77</td>
<td>0.358</td>
<td>4.75</td>
</tr>
<tr>
<td>HA-P 1:1 WD</td>
<td>353.36</td>
<td>41.75</td>
<td>0.154</td>
<td>282.47</td>
</tr>
<tr>
<td>HA-P 1:1 CD</td>
<td>72.74</td>
<td>30.50</td>
<td>0.185</td>
<td>51.10</td>
</tr>
<tr>
<td>HA-P 1:4 WD</td>
<td>1467.00</td>
<td>73.52</td>
<td>0.142</td>
<td>1095.97</td>
</tr>
<tr>
<td>HA-P 1:4 CD</td>
<td>701.66</td>
<td>47.50</td>
<td>0.112</td>
<td>496.80</td>
</tr>
</tbody>
</table>
sample 1:4 HA-P WD exhibited the highest $S$ values, which must be attributed to the strongest structures that are closest to covalent gels.

These findings are in agreement with mechanical spectra data that indicate that the drug incorporation resulted in the weakening of polymer network due to factors previously discussed.

The creep-recovery tests were performed to assist the understanding of the internal structures of these systems that presented an important elastic behavior as showed by mechanical spectra. The recovery (%) was calculated from $J_{\text{max}}$ and $J_{\text{min}}$ values (Table 2), according to an equation proposed by Ghannam (2004):

$$R(\%) = \left[ \frac{J_{\text{max}} - J_{\text{min}}}{J_{\text{max}}} \right] \times 100$$

The highest $R\%$ values of 1:4 samples show that WD and CD samples, containing higher relative amount of pectin, are more elastic than the others, corroborating the $G'$ data, demonstrating that the increase of pectin content allows the formation of stronger and more elastic gels. Besides, the differences in creep-recovery data...
for samples WD and CD show that internal structures are different (Dolz, Hernandez, & Delegido, 2008), which also should be related to drug–polymer interactions.

4. Conclusions

The influence of both drug loading and polymer proportion on microparticles properties was demonstrated and the drug–polymer interactions were evidenced by the analytical results presented in this work. In addition, it was demonstrated that the drug loading resulted in an increase of both thermal stability and crystallinity degree, but with a decrease of mechanical strength of the structures. Likewise, the microparticles properties were sensitive to polymer proportion, since the blends with higher levels of pectin resulted in higher thermal stability, while the rheological properties, generally, pointed to the strengthening of the structures.

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References


Fig. 5. Mechanical spectra of samples.


