Original Research Paper

Insights into the swelling process and drug release mechanisms from cross-linked pectin/high amylose starch matrices

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ABSTRACT

Cross-linked pectin/high amylose mixtures were evaluated as a new excipient for matrix tablets formulations, since the mixing of polymers and cross-linking reaction represent rational tools to reach materials with modulated and specific properties that meet specific therapeutic needs. Objective: In this work the influence of polymer ratio and cross-linking process on the swelling and the mechanism driving the drug release from swellable matrix tablets prepared with this excipient was investigated. Methods: Cross-linked samples were characterized by their micromeritic properties (size and shape, density, angle of repose and flow rate) and liquid uptake ability. Matrix tablets were evaluated according their physical properties and the drug release rates and mechanisms were also investigated. Results: Cross-linked samples demonstrated size homogeneity and irregular shape, with liquid uptake ability insensible to pH. Cross-linking process of samples allowed the control of drug release rates and the drug release mechanism was influenced by both polymer ratio and cross-linking process. The drug release of samples with minor proportion of pectin was driven by an anomalous transport and the increase of the pectin proportion contributed to the erosion of the matrix. Conclusion: The cross-linked mixtures of high amylose and pectin showed a suitable excipient for slowing the drug release rates.

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1. Introduction

The preparation of new materials for development of drug delivery systems that allow the control of drug release rates according to the specific therapeutic needs represents an important subject of research in the pharmaceutical sciences field.

The use of blends of already known polymers represents a rational strategy to reach new materials with distinct properties that can be modulated according to specific uses [1–7], avoiding the great majority of the costs involved in the synthesis and characterization of a completely new material. In this sense, simple changes in polymers ratio can result in a wide range of physicochemical properties that may provide different drug delivery patterns [2].

Hydrogels are hydrophilic polymers that absorb high amounts of water and its increased use in the drug delivery systems formulations is based on its ability to origin a gel network in the swollen state which entraps the drug and acts as a barrier to its release to the medium. In this way, the swelling ability of hydrogels is a fundamental property that should influence the drug release rates, by controlling both the diffusion rate of the penetrant into the matrix and the drug dissolution and diffusion throughout the gel layer of the swollen matrix [8–12].

Starch is a natural polysaccharide composed by amylose, representing the linear fraction of this macromolecule, while amylopectin is highly branched fraction. High amylose, a modified starch containing 70% of amylose, has been used successfully in the research and development of swellable hydrophilic matrices and many studies report their improved properties for controlled drug delivery purposes in relation to conventional starch [12–20].

Moreover, some properties of high amylose starch, such as solubility, swelling, rheological behavior, gel and film formation, and biodegradation rate can be modified via esterification, etherification and oxidation of its hydroxyl groups [12]. In fact, cross-linking has been shown to be a key technique for modifying polysaccharides properties and can be achieved by adding intra- and inter-molecular bonds [21,22].

The successful use of high amylose starch cross-linked by different chemicals, such as epichlorohydrin and sodium trimetaphosphate (STMP), for control of drug release rates in the development of different controlled drug delivery systems have been demonstrated [14,18,23–26]. High amylose cross-linked with STMP at different degrees, by varying base strength (2% or 4%) and contact time (0.5–4 h), was used as excipient of solid non-compacted systems and according to cross-linking degree the drug release rates were controlled until 18 h [18].

Pectin is a polysaccharide that has been currently used, modified or not, in the composition of hydrophilic matrices and other drug delivery systems, since it is able to form matrix or reservoir systems and exhibits promising mucoadhesive and swelling properties that may lead to an effective control over drug delivery rate [27–33].

Blends of pectin and chitosan were used in preparation of zinc–pectin–chitosan composites intended to colon-specific drug delivery of resveratrol and the colon-specific drug release was reached [34].

In other work, blends of high amylose and pectin were exploited for preparing microparticles that exhibited increased encapsulation efficiency and decreased drug dissolution in the simulated gastric condition (pH 1.2) in relation to pectin-based microparticles [35].

The improvement of mechanical properties of dispersions of blends of the conventional starch and pectin cross-linked by STMP in relation to isolated polymer was also demonstrated [36].

Blends of pectin–high amylose starch cross-linked with STMP in alkaline medium were early synthesized and characterized by Carbinatto et al. (2012) [7] and the set of the results shown that the cross-linking reaction allowed the building of covalent gels with improved thermal and physical stability, making this material a promising excipient for the design of controlled drug release systems based on hydrogel matrices.

The drug release throughout the swellable polymer matrices can be very complex and the understanding of the different mechanisms involved in this process is fundamental for the rational design of drug delivery systems that can fulfill the different therapeutic needs, by fitting the desired spatial and time drug release schedules.

In this work, blends of high amylose and pectin cross-linked with STMP at different degrees were evaluated as excipient of hydrophilic matrix tablets and the influence of cross-linking degree and polymers ratio on the drug release patterns and mechanisms was evaluated.

2. Materials and methods

2.1. Materials

Pectin (type LM-56CS) was provided from CP Kelco (Brazil), high amylose (Hylon VII, 70% amylose, 30% amylopectin) was obtained from National Starch & Chemical (New Jersey, USA), STMP was purchased from Sigma–Aldrich Co., (St. Louis, USA), sodium hydroxide (NaOH) was supplied by Grupo Quimica (Brazil), hydrochloric acid was provided by Quimis (Brazil), and nimesulide and sodium lauryl sulfate were from Henrifarma (Sao Paulo, Brazil).

2.2. Cross-linking of polymers

Cross-linking of polymers was performed according to procedure described in our previous paper [7].

Pectin and high amylose starch mixed at different mass ratios (1:4, 1:1 and 4:1) were cross-linked with STMP (30% of the polymer mass) at room temperature. Different degrees of cross-linking were achieved by varying the base (NaOH) concentration (2% and 4%) and the pectin/high amylose starch/NaOH/STMP contact time (1, 2 and 4 h). After the reaction time, all samples were treated with the adequate amount of 1 mol/l HCl in order to set the pH at 6. The solids were separated by vacuum filtration and washed repeatedly with ethanol of different concentrations (85 GL, 65 GL and 96 GL). The final product was dried at room temperature for 24 h, pulverized and sieved (sieve opening 0.97 mm). The samples...
were labeled according to the polymer mixture ratio (pectin-high amylose)—base strength—cross-linking reaction time; samples without cross-linker received a W suffix as presented in Table 1.

2.3. Size and shape properties

Size distribution analysis was performed by using a Motic Images Advance 3.2 image analyzer coupled to a Leica MZ APO™ microscope. The parameters Feret diameter at 0° and circularity of at least 100 particles were measured in order to evaluate the particle size distribution and shape, respectively.

2.4. Liquid uptake

The dynamics of media uptake was determined on an Enslin’s device [18,37]. For the assay, 0.05 g of powdered samples was poured onto the sintering filter and the volume of media absorbed by the sample after predetermined times was measured with the graduated pipette of the device. Different pH media were assayed in order to simulate the segments of GI tract: 0.1 N hydrochloric acid, pH 2.0 and phosphate buffer pH 7.4, all of them without enzymes. The assays were carried out in triplicate and the results expressed as liquid uptake (%) in relation to the initial mass of the samples. Statistical analysis of the results was performed by ANOVA/Tukey with a significance level <0.05.

2.5. Bulk and tapped apparent densities

The bulk apparent density (d_b) and tapped apparent density (d_t) were indirectly evaluated from apparent volume (V) and tapped volume (V_t) measurements. Initially, about 10 g (m) of samples 11-4-2, 14-4-2, pectin and high amylose starch were carefully introduced into a 25 ml graduated cylinder and the bulk volume was measured. Thus, the samples were submitted to cycles of 1250 taps on an automatic volumeter tester (Volumeter Tapped, model SVM, ERWEKA, Heusenstamm, Germany) until volume difference in relation to the previous measurement was lesser than 2%. The values of d_b and d_t were calculated according to equations (1) and (2):

\[
d_b = \frac{m}{V}
\]

\[
d_t = \frac{m}{V_t}
\]

2.6. Angle of repose and flow rate

The angle of repose was determined according to the free base cone technique [38]. An accurately weighed mass (20 g) of samples 11-4-2, 14-4-2, pectin and high amylose starch was introduced into a stainless steel funnel (1.2 cm opening) coupled to a vibrating device. The orifice of the funnel was opened and the powder flowed onto a flat surface. The cone basis and height were measured and the \( \alpha \) angle was calculated by equation (3). The time the whole powder mass spent to flow down was measured in order to determining the flow rate.

\[
tg \alpha = \frac{h}{r}
\]

\( h \) = cone height (cm) and \( r \) = cone radius (cm).

2.7. Preparation of matrix tablets

The 11-4-2 and 14-4-2 samples were selected as carrier polymer for tablets preparation, since according to rheological data [7] and swelling properties, they were considered as the most promising materials to control the drug release rates. The tablets were produced in an eccentric tablet machine (Erweka® AR 400) equipped with a 10 mm flat punch and die set that was manually filled with a mixture of polymer carrier (250 mg) and nimesulide (100 mg), by applying sufficient compression force to prepare tablets with hardness of 110 N. Tablets containing carrier treated without cross-linker (with W suffix) in the same proportion drug:carrier and drug raw (100 mg) were also prepared under same conditions.

2.8. Physical properties of tablets

Physical properties of tablets were determined based on pharmacopeial specifications [38]. Weight variation of 40 tablets was measured on an analytical balance (Owa Labor). For the friability test, 20 tablets of each sample were submitted to 100 revolutions in a friabulator (type TA 20 (Erweka®)). The hardness of 10 tablets of each sample was evaluated by measuring the radial breaking force on a hardness tester (Schleuniger Pharmatron® — type 6D).

2.9. “In vitro” drug dissolution

The in vitro dissolution patterns of tablets containing 100 mg of nimesulide and 250 mg of carrier polymer (11-4-2, 14-4-2, 11-4-2W, 14-4-2W) were performed on a Hanson Research (New Hanson SR-8 Plus) dissolution station equipped with apparatus I (basket), at 50 rpm. The dissolution tests were performed in media with different pH values in order to simulate the pH of different segments of GI tract, based on the USP 31 [38] specifications for delayed release dosage forms test, with minor modifications. The first step of the test was performed in 750 ml of hydrochloric acid 0.1 N pH 2.0 (simulated gastric media), during 120 min. Then, the pH was changed to 7.4 (simulated small intestine fluid) by adding 250 ml of 0.2 M sodium phosphate tribasic. All media were added by 0.5% sodium lauryl sulfate as surfactant due to the low solubility of nimesulide in the gastric pH. The
temperature was controlled at 37 °C and the samples were collected at pre-determined times. The drug concentration was quantified by measuring the absorbance at 297 nm and 298 nm (Hewlett Packard-Kayak XA) in gastric and enteric media, respectively. Tablets containing 100 mg of nimesulide (drug raw) were tested as control.

2.10. Analysis of kinetic models

Drug dissolution data were fitted with different mathematical models (Table 2) (Sigma Plot 10.0). All equations were fitted to the whole dissolution curves, except for Peppas and Weibull equations fitted only until 60% of data.

3. Results and discussion

3.1. Particle size distribution

For all reaction conditions, the 4:1 and 1:1 samples presented the narrowest size distribution (200–700 μm) while 1:4 samples reached 800 μm. However, the major size frequency of all samples was observed in the 300–500 μm range. These similar particle size features can be related to some homogeneity of structures, so that when the stress is applied in comminution process, the fissures are distributed in a somewhat homogeneous manner throughout the fragile points of polymer network, avoiding the occurrence of particles with extreme sizes [18]. In order to corroborate the size distribution data, the Feret diameter of samples were determined and their values were between 325.46 and 414.07 μm, confirming the size homogeneity of the particles. The circularity values between 0.599 and 0.746 demonstrate that the particles present irregular shape.

3.2. Liquid uptake

The swelling degree is an important property to be evaluated in hydrophilic polymers used in controlled drug delivery systems because it is correlated with the diffusion rates of both the penetrant into the matrix and the drug throughout the gel layer of the matrix [8,20,31,39–41]. Besides, structural changes due to cross-linking degree and the drug release behavior of different materials can be evidenced by swelling behavior of them [18].

The values of liquid uptake (%) in media with different pH values (0.1 N HCl, phosphate buffer pH 7.4) are shown in Fig. 1, in which it can be observed that samples prepared with NaOH 2% presented higher swelling ability than samples prepared with NaOH 4%. However, the swelling behavior of all samples was not sensible to pH variation (p < 0.05).

The samples prepared with 2% NaOH at 4:1 polymer proportion exhibited the highest swelling degree, since the most hydrophilic polymer (pectin) is in greater proportion, favoring the swelling [20,42]. The lower swelling ability of samples prepared with 4% NaOH can be attributed to the high cross-linking degree of these samples, such that the mesh size of polymer network limits the water entrance in the polymer structure. Besides, the inter-chains ester linkages of cross-linked samples can restrict the motion of chains, affecting the liquid diffusion throughout of them [18,25]. Additionally, it should be evidenced that the samples 11-4-2 and 14-4-2, which exhibited the lowest water uptake values were those that presented the highest values of G’ (elastic modulus) [7], findings that corroborate the achievements about the highest cross-linking degree of these samples.

3.3. Apparent densities

The density of a powdered solid influences the flow, so that denser powders present better flow properties [43,44]. The values of bulk and packed densities of materials were between 0.5 and 0.8 g/ml (Table 3). According to values presented in Table 3, the samples containing higher proportion of high amylose showed lower density, certainly due to the low density of this polymer itself. The cross-linking process influenced the density of 1:1 and 1:4 samples, promoting the densification of them, which can be seen by their higher density values in relation to the isolated polymers, since the cross-linking process allow a more packed polymer network.

3.4. Flow properties

The angle of repose and the flow rate are parameters that describe the flow ability of materials [43,45,46]. Pectin, 11-4-2 and 14-4-2 samples presented repose angles values between 20 and 30° (Table 3) while the high amylose value was 39.9°. The results of repose angle indicated that, generally, the samples presented free flow behavior while the highest angle value of high amylose demonstrates its flow deficiency [46].

The values of flow rate of pectin and high amylose were 2.542 and 0.491, respectively, while the cross-linked samples values were 13.95 g/s (11-4-2) and 11.068 g/s (14-4-2). The higher flow rate values of cross-linked samples confirm that their higher densities favored the flow ability.

3.5. Physical properties of tablets

The values of weight variation, hardness and friability of tablets were 2.57% and 1.66%, 118.7 N and 159.9 N and 0.12% and 0.13% for samples 11-4-2 and 14-4-2, respectively.

The results of all physical parameters of tablets are in agreement with pharmacopeial specifications [38]. The low weight variation of tablets (2.57% and 1.66% for 11-4-2 and 14-4-2, respectively) is consistent with the free flow properties of cross-linked samples that contribute to regular filling of die and punch set.

<table>
<thead>
<tr>
<th>Table 2 – Release mathematical models.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
</tr>
<tr>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Baker and Lonsdale</td>
</tr>
<tr>
<td>First order</td>
</tr>
<tr>
<td>Higuchi</td>
</tr>
<tr>
<td>Hixson and Crowell</td>
</tr>
<tr>
<td>Peppas</td>
</tr>
<tr>
<td>Weibull</td>
</tr>
</tbody>
</table>

<sup>a</sup> F = amount of drug release at time t; k<sub>RL</sub>, k<sub>H</sub>, k<sub>c</sub>, k<sub>P</sub>, and k<sub>b</sub> – release rate constants for different equations; n and b = release exponents.
3.6. **In vitro drug dissolution patterns**

The drug release from swellable hydrophilic matrices can be controlled by physical and chemical processes, involving the liquid penetration within the polymer network, the swelling of hydrated polymer, drug diffusion throughout swollen matrix and, sometimes, its erosion [31,47].

The in vitro drug dissolution patterns from tablets are showed in Fig. 2 and Table 4 shows that raw drug was fully released in 1.5 h of test while the cross-linked samples 11-4-2 and 14-4-2 released 22.77% and 21.41%, respectively, in the same time. The samples prepared without cross-linker (11-4-2W and 14-4-2W) presented release rates about 1.3 times faster than their cross-linked counterparts.

The lowest drug release rates exhibited by cross-linked samples (11-4-2 and 14-4-2) demonstrate that the inter-chains ester linkages introduced to the polymer structure by cross-linking reaction should result in a more rigid structure, which originates a more elastic and denser swollen matrix, restricting the motion of chains [6,48,49]. This more viscous physical barrier retards the drug diffusion and thus, the drug release rates decrease.

In the acidic media, the lowest drug release (%) of 11-4-2 sample indicates that due to the higher pectin proportion present in this sample, a more viscous and thicker gel layer can be built, which represents a more resistant barrier against drug diffusion [30,50].

However, in simulated enteric medium (pH 7.4), this sample exhibited the highest drug release rates, which can be attributed to the increased solubility of pectin at this higher pH value, making the drug release faster [27,35,51]. This behavior is highlighted by 11-4-2W sample, since a sharp increase of drug release rates also occurred in this higher pH.

Besides, in increased pH, the deprotonation and ionization of sulfonanilide group of nimesulide enhance its solubility [52], which can also favor the dissolution process.

### Table 3 — Values of flow rate, angle of repose, bulk and tapped densities.

<table>
<thead>
<tr>
<th></th>
<th>Pectin</th>
<th>High amylose</th>
<th>11-4-2</th>
<th>14-4-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow rate (g/s)</td>
<td>2.542 ± 0.231</td>
<td>0.491 ± 0.577</td>
<td>13.95 ± 0.029</td>
<td>11.068 ± 0.011</td>
</tr>
<tr>
<td>Repose angle (°)</td>
<td>20.02 ± 0.015</td>
<td>39.94 ± 0.040</td>
<td>20.98 ± 0</td>
<td>26.25 ± 0</td>
</tr>
<tr>
<td>dₙ (g/ml)</td>
<td>0.607 ± 0.004</td>
<td>0.502 ± 0.002</td>
<td>0.704 ± 0</td>
<td>0.558 ± 0.002</td>
</tr>
<tr>
<td>dₜ (g/ml)</td>
<td>0.769 ± 0</td>
<td>0.588 ± 0</td>
<td>0.817 ± 0.003</td>
<td>0.670 ± 0.003</td>
</tr>
</tbody>
</table>
3.7. Analysis of kinetic models

The fitting of drug release data by appropriate mathematical models that support the interpretation and comprehension of the mechanisms involved in the control of drug release process is a powerful tool to modulate the release features according to specific therapeutic needs.

Different mathematical models (Table 2) were applied to in vitro drug dissolution profiles and their respective coefficients were estimated (Table 5). According to \( r^2 \) values (Table 5) it can be noted that the 11-4-2 and 11-4-2W samples fitted better with the Weibull model while the 14-4-2 and 11-4-2W samples do it with the Peppas model.

The samples 14-4-2 and 11-4-2W fitted better with Peppas model that is based on the Power Law, which establish an exponential correlation between drug release and time; and it must be fitted only to the first 60% of drug release [53–55].

For Peppas model, the value of release exponent (\( n \)) is correlated with mechanism that drives the drug release process and \( n \) release exponent values of studied samples presented between 0.4716 and 0.8628 (Table 5) that characterize an anomalous transport for cylindrical shaped samples (Table 6) [56].

The \( b \) coefficients values of the Weibull are correlated with the release mechanism of drug throughout the polymer matrix (Table 6). Thus, values lower than 0.75 are related to Fickian diffusion, while \( b \) values between 0.75 and 1.0 suggest that release is governed by Fickian diffusion and case II transport (swelling). The 11-4-2 and 14-4-2W samples presented \( b \) coefficient values higher than 1 (Table 5). Therefore drug release is driven by complex mechanism, where swelling plus erosion of matrix and diffusion of drug take place concomitantly [45].

On the other hand, the release data of the samples 11-4-2 and 14-4-2W presented better correlation with the Weibull

![Fig. 2 – In vitro drug release profiles.](image)

Table 4 – In vitro nimesulide released (%).

<table>
<thead>
<tr>
<th>Samples</th>
<th>Nimesulide released (%)</th>
<th>0.5 h</th>
<th>2 h</th>
<th>2.5 h</th>
<th>4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-4-2</td>
<td>13.79</td>
<td>23.88</td>
<td>47.34</td>
<td>59.07</td>
<td></td>
</tr>
<tr>
<td>11-4-2W</td>
<td>17.97</td>
<td>36.11</td>
<td>95.88</td>
<td>100.20</td>
<td></td>
</tr>
<tr>
<td>14-4-2</td>
<td>9.02</td>
<td>26.47</td>
<td>38.77</td>
<td>51.88</td>
<td></td>
</tr>
<tr>
<td>14-4-2W</td>
<td>14.14</td>
<td>31.25</td>
<td>48.07</td>
<td>79.42</td>
<td></td>
</tr>
</tbody>
</table>

Table 5 – Release coefficients for nimesulide fitted with different mathematical models.

<table>
<thead>
<tr>
<th>Release models</th>
<th>Samples</th>
<th>11-4-2</th>
<th>14-4-2</th>
<th>11-4-2W</th>
<th>14-4-2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker and Lonsdale</td>
<td>( r^2 )</td>
<td>0.8724</td>
<td>0.8052</td>
<td>0.7018</td>
<td>0.8049</td>
</tr>
<tr>
<td></td>
<td>( k )</td>
<td>0.0004</td>
<td>0.0003</td>
<td>0.0008</td>
<td>0.0006</td>
</tr>
<tr>
<td>Hixson and Crowell</td>
<td>( r^2 )</td>
<td>0.9250</td>
<td>0.9622</td>
<td>0.8560</td>
<td>0.9521</td>
</tr>
<tr>
<td></td>
<td>( k )</td>
<td>0.0013</td>
<td>0.0010</td>
<td>0.0024</td>
<td>0.0016</td>
</tr>
<tr>
<td>Higuchi</td>
<td>( r^2 )</td>
<td>0.8263</td>
<td>0.8552</td>
<td>0.7787</td>
<td>0.8805</td>
</tr>
<tr>
<td></td>
<td>( k )</td>
<td>4.1734</td>
<td>3.5891</td>
<td>5.8372</td>
<td>4.8173</td>
</tr>
<tr>
<td>First-order</td>
<td>( r^2 )</td>
<td>0.8936</td>
<td>0.9424</td>
<td>0.8185</td>
<td>0.9198</td>
</tr>
<tr>
<td></td>
<td>( k )</td>
<td>0.0044</td>
<td>0.0036</td>
<td>0.0084</td>
<td>0.0058</td>
</tr>
<tr>
<td>Peppas</td>
<td>( r^2 )</td>
<td>0.9664</td>
<td>0.9943</td>
<td>0.9946</td>
<td>0.9723</td>
</tr>
<tr>
<td></td>
<td>( k )</td>
<td>0.4710</td>
<td>0.4673</td>
<td>3.7362</td>
<td>1.4487</td>
</tr>
<tr>
<td></td>
<td>( n )</td>
<td>0.8800</td>
<td>0.8628</td>
<td>0.4716</td>
<td>0.6668</td>
</tr>
<tr>
<td>Weibull</td>
<td>( r^2 )</td>
<td>0.9872</td>
<td>0.9931</td>
<td>0.9492</td>
<td>0.9945</td>
</tr>
<tr>
<td></td>
<td>( k )</td>
<td>136.3908</td>
<td>35,726.536</td>
<td>102.9414</td>
<td>100.8062</td>
</tr>
<tr>
<td></td>
<td>( b )</td>
<td>3.0144</td>
<td>1.2113</td>
<td>426,408.9007</td>
<td>10.2841</td>
</tr>
</tbody>
</table>

Table 6 – Correlation between release exponent (\( n \)) values for the Korsmeyer – Peppas equation and drug release mechanisms depending on the geometry shape [42].

<table>
<thead>
<tr>
<th>Release exponent (( n ))</th>
<th>Thin film</th>
<th>Cylindrical</th>
<th>Sphere</th>
<th>Release mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.45</td>
<td>0.43</td>
<td></td>
<td>Fickian diffusion</td>
</tr>
<tr>
<td>0.5 &lt; ( n &lt; 1.0 )</td>
<td>0.45 &lt; ( n &lt; 0.89 )</td>
<td>0.43 &lt; ( n &lt; 0.85 )</td>
<td></td>
<td>Anomalous transport</td>
</tr>
<tr>
<td>1.0</td>
<td>0.89</td>
<td>0.85</td>
<td></td>
<td>Case II transport</td>
</tr>
</tbody>
</table>

The values of \( n \) between 0.45 and 0.85 indicate an anomalous transport.
model and their respective b exponent values (Table 5) pointed to a complex mechanism of drug release in which diffusion, swelling and erosion of polymer matrix are involved in the drug release process [57].

The change of drug release behavior of sample 11-4-2 in relation to sample 14-4-2 can be attributed to the highest pectin proportion in the former sample, since the more hydrophilic nature of this polymer must have contributed to an effective dissolution of swollen polymer matrix, making the erosion takes place in drug release process, accelerating the drug release rates in the simulated enteric medium.

Moreover, the change of release mechanisms between 14-4-2 and 14-4-2W samples also indicated that for samples containing the lowest pectin proportion, the cross-linking reaction allow the building of a more cohesive matrix, preventing the erosion of the system.

4. Conclusions

The blends of high amyllose and pectin cross-linked with sodium trimetaphosphate shown to be a promising excipient for swellable matrix tablets intended to controlled drug delivery systems. Samples prepared with 2% of base, containing higher proportion of pectin, showed higher swelling ability, while for samples prepared with 4% NaOH this property was limited by the high cross-linking degree that restricts the motion of polymer chains and decrease the size of polymer mesh. The cross-linking reaction was an effective tool to control the drug release rates and the mathematical models indicated that increase of pectin proportion change the mechanism that drive the drug release process, allowing the erosion of the system.

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