Utilization of Natural Polyelectrolytes in the Preparation of Naproxen as Sustained Release Matrix Tablet

Zahraa Oleiwi Hamzah*, Wedad k. Ali*
*Department of Pharmaceutics, College of Pharmacy, Mustansiriyah University/ Iraq

Abstract:

Our study demonstrates the preparation of naproxen as a sustained release matrix tablet using polyelectrolyte complexes PECs. The cationic polymer used in this study is chitosan CS while the anionic polymer includes sodium alginate SA, xanthan gum XG or carrageenan CG as anionic polymers. FT-IR spectra of these complexes were studied to indicate the interactions between polyions. Precompression and compression parameters were studied including the flowability, tablet hardness, thickness, friability, weight variation, drug content and in vitro release study. The results showed that the release rate of naproxen was decreased in the formulas that contains the physical mixtures comparing to the formulas with single polymer and the formula containing high molecular weight chitosan: xanthan gum CSh: XG physical mixture in 3:1 ratio formed the strongest PEC in which the release rate extended up to 20 hr. In conclusion, this work succeeded in preparation of naproxen as oral sustained release matrix tablet, using a physical mixture of cationic and anionic polymers to form PECs resulting in less frequent dosing and a reduction in gastric irritation.

Key words: naproxen, polyelectrolyte complex, sustained release, chitosan, xanthan gum, sodium alginate, carrageenan.

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Corresponding Author email: pharm.dr.wedad.ali@uomustansiriyah.edu.iq
orcid: https://orcid.org/0000-0003-2522-5428

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This study demonstrates the preparation of naproxen as a sustained release matrix tablet using polyelectrolyte complexes (PECs). The cationic polymer used in this study is chitosan (CS) while the anionic polymer includes sodium alginate (SA), xanthan gum (XG) or carrageenan (CG) as anionic polymers. FT-IR spectra of these complexes were studied to indicate the interactions between polyions. Precompression and compression parameters were studied including the flowability, tablet hardness, thickness, friability, weight variation, drug content and in vitro release study. The results showed that the release rate of naproxen was decreased in the formulas that contain physical mixtures comparing to the formulas with single polymer and the formula containing high molecular weight chitosan: xanthan gum (CSh): XG physical mixture in 3:1 ratio formed the strongest PEC in which the release rate extended up to 20 hr. In conclusion, this work succeeded in preparation of naproxen as oral sustained release matrix tablet, using a physical mixture of cationic and anionic polymers to form PECs resulting in less frequent dosing and a reduction in gastric irritation.

Key words: naproxen, polyelectrolyte complex, sustained release, chitosan, xanthan gum, sodium alginate, carrageenan.
**Introduction:**

The Polyelectrolyte complexes (PECs) have an important role in the pharmaceutical preparations especially in the preparation of matrix tablets due to their property of extending the drug release\[1\]. PECs are prepared by combining macromolecules of opposite charges in solution. The formation of these complexes is affected by many factors such as molecular weight, ionic strength, charge density, the type and concentration of salt in the solution, pH and the intensity of mixing\[2\].

Different methods have been used to study the interaction among polymers including measurement of turbidity, measurement of pH, ionic strength, viscosity, light scattering, infrared spectroscopy (IR), Nuclear Magnetic Resonance (NMR), thermal analysis, pKa and powder X-Ray diffraction \[3\]. Chitosan a polycationic derivative of poly-N-acetyl-D-Glucosamine (chitin), it is widely used in various applications such as gels, solutions, films and fibers\[4\]. Anionic polymers like (pectin, alginate, carrageenan, xanthan gum and carboxymethyl cellulose) can form PECs with the polycation chitosan for extending drug delivery systems \[5\].

Recently, researchers have gained interest in the preparation of different PECs such as chitosan/carbopol and chitosan/pectin PECs which required acetic acid to be formed \[6\] \[7\]. These methods have many disadvantages such as energy-consuming and the presence of acetic acid; Therefore, many researchers suggested preparation of polyelectrolyte complex from cationic polymer CS and anionic polymer of SA, XG and CG using physical mixtures without the need of the addition of acetic acid since the PECs will form as a film on the surface of the tablet in the stomach after tablet administration. The electrostatic interaction between NH4+ group in CS and COO− in SA, XG and CG possibly occurs when the pH of the media is about 1.2 \[8\] \[9\].

Naproxen is a weak acid [(+)-(S)-2-(6-methoxynaphthalen-2-yl) propanoic acid] with pKa of 4.2\[10\]. Naproxen is a NSAID used in the treatment of rheumatoid arthritis and in the relief of pain in cases like headaches \[11\]. High levels of naproxen in the stomach can cause stomach ulcer and bleeding\[12] \[13\].

In this study, different types of anionic electrolyte were physically mixed separately at different weight ratios with CS and other excipients then directly compressed to prepare sustained release PECs matrix tablet for naproxen. In order to confirm the electrostatic interactions between (CS/SA), (CS/XG) and (CS/CG), tablets were dried and analyzed by FT-IR spectroscopy.

The results of this study showed that naproxen can be formulated as PECs matrix tablets, and that the release of naproxen from these matrix tablets was sustained. Thus, these sustained release tablets could be used as oral tablets for naproxen to reduce the frequency of dose with less gastric irritation.

**Materials and Methods**

**Materials:**

Naproxen powder, high molecular weight chitosan CS, carrageenan CG, polyvinyl pyrrolidone PVP and lactose monohydrate were supplied by (Guokang Bio-Technology, China), sodium alginate SA and xanthan gum XG were provided by (Wuhan Senwayer century, China), magnesium stearate was supplied by (Scharlab S.L, Spain).

**Methods:**

**Preparation of Sustained Release Matrix Tablet of Naproxen**

Different formulas were prepared as shown in (table 1) and compressed into tablets using direct compression method to produce a 250 mg naproxen sustained release matrix tablets in which the total
weight of each tablet was 500 mg. The formulas were prepared using different polymers (CS, SA, XG and CG) separately as a single polymer and as a physical mixture of two polymers to produce a polyelectrolyte mixture, in addition to other excipients. The powders of each formula were mixed for 15 minutes; the resultant mixture was mixed with magnesium stearate (0.5% w/w) for 1 minute and compressed by manual tablet machine (Riva minipress, Germany) into 500 mg tablet.

**Table (1) Different formulas of naproxen as sustained release tablets**

<table>
<thead>
<tr>
<th>Formula No.</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>F10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance</td>
<td>Naproxen</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td></td>
<td>CS₄₈</td>
<td>100</td>
<td>50</td>
<td>150</td>
<td>50</td>
<td>200</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SA</td>
<td>100</td>
<td>100</td>
<td>50</td>
<td>150</td>
<td>200</td>
<td>50</td>
<td>200</td>
<td>50</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>XG</td>
<td>50</td>
<td>200</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Magnesium Stearate</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>Lactose monohydrate</td>
<td>22.5</td>
<td>72.5</td>
<td>22.5</td>
<td>22.5</td>
<td>22.5</td>
<td>22.5</td>
<td>22.5</td>
<td>22.5</td>
<td>22.5</td>
</tr>
<tr>
<td></td>
<td>Total Weight (mg)</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
</tbody>
</table>


**Fourier Transform Infrared Study (FT-IR)**

Powder about 1 mg of different types of polymer used in this study was mixed separately with 200 mg KBr and compressed into disc using hydrolytic press.

The FT-IR spectra of CS, CG, XG, SA, (CS/CG) PEC, (CS/XG) PEC and (CS/SA) PEC were obtained using potassium bromide disks in the range of 4000-400 cm⁻¹ (Bruker- tensor27, Europe) to confirm complex formation between those polymers.

**Precompression Evaluation of Mixture Flow Properties**

**Angle of Repose**

The determination of angle of repose was made by using fixed funnel with free standing core method which implies securing the funnel with its tip at a specific height (H) on a distance of a graph paper on a flat surface, then pouring the powder through the funnel up till the apex of conical pile is touching the funnel tip.

\[
\tan \theta = \frac{H}{R}
\]

Where:

- H = The height.
- R = The radius of the powder cone.

**Tapped Density and Bulk Density Measurement**

The determination of bulk density was made by pouring the blended powder into graduated cylinder:

Bulk density = Weight of sample/Bulked volume

While, tapped density was measured by a cylinder which contains the blend of a
known mass and tapping at specific time as follows: 
Tapped density = Sample weight / Tapping volume

**Carr’s index or % compressibility**[^17]
An index signifies the flow properties of the powder and written as percentage:

\[
I = 100 \times \left( \frac{D_{\text{tap}} - D_{\text{bulk}}}{D_{\text{tap}}} \right)
\]

Where:
- \(D_{\text{tap}}\) = The tapped density of powder
- \(D_{\text{bulk}}\) = The bulk density of the powder

**Hausner ratio**[^17]
An index that’s indirectly measuring the easiness of the flowability of powder:

Hausner’s ratio = Density \(\frac{\text{tap}}{\text{bulk}}\)

**Post Compression Evaluation of Naproxen Sustained Release Matrix Tablet**

**Hardness Test**
The hardness of 3 tablets from each formula was recorded individually by using Monsanto type hardness tester. The average value of the hardness (kg/cm²) ± SD was measured[^18].

**Friability Test[^19]**
Determination of friability was made by using Roche friabilator and written as a percentage. 10 tablets were taken and weighted for revolving for 4 minutes at 25 rpm. After removing the fines, tablets weighed again to calculate the losing of weight as follows:

\[
F = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100
\]

**Thickmess Test**
A vernier caliper was used to determine the thickness of three tablets of each formula and the average value was recorded[^20].

**Weight variation**
Selection of 20 tablets randomly then weighed individually to be compared with the average weight for weight variation listed in USP.

**Drug Content**
Ten tablets of naproxen from F3 were randomly selected and grinded into powder in a mortar and a weighed amount equivalent to 250 mg was solubilized in phosphate buffer 6.8, up to 100 ml. Several aliquots were taken to be filtered by using 0.45 μm millipore and assayed by UV-Spectrophotometer at 271 nm. The procedure was done in triplicate and the average result was chosen[^6][^21].

**In vitro Release Study**
The release properties of naproxen sustained release matrix tablets were investigated using USP dissolution apparatus I (basket) at 37 ± 0.5 °C with rotation speed of 100 rpm in 900 ml dissolution medium (HCl solution 1.2) for 2 hours and (phosphate buffer 6.8) at specific times intervals (0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20) hour(s) in which samples of 5 ml were withdrawn and the volume of samples was replaced with 5ml of the same buffer solution. These samples were filtered using 0.45 –μm millipore filter and analyzed spectrophotometrically at 271 nm for the drug content in both mediums. Each test was done in triplicate[^22][^23].

**Results and discussion**

**Fourier Transform Infrared (FT-IR) Spectroscopy**
The electrostatic interaction between NH₃⁺ group in CS and COO⁻ in SA, XG and CG lead to the formation of self-assembled PECs as a film on the surface of the tablet in the dissolution process when the pH of the solution was about 1.2[^8][^9].
In order to confirm the (CS/SA), (CS/XG) and (CS/CG) interactions, tablets were placed in dissolution media for 3 hrs. and then removed, dried and analyzed by FT-
IR spectroscopy. Figures (1, 2 and 3) show the FT-IR spectra of each complex. In CS, the bands were shifted 1600.01 cm$^{-1}$ for (C=O) group in the spectrum of (CS/SA) PEC. While in (CS/XG) PEC spectra the bands of CS were shifted to 1545.30 cm$^{-1}$ for (C=O) group. In addition (CS/CG) PEC spectra showed the shifting of CS bands to 1541.50 cm$^{-1}$ for (C=O) group. The IR spectrum of SA, XG and CG showed the characteristics peaks at 1611.70 cm$^{-1}$, 1602.21 cm$^{-1}$ and 1631.29 cm$^{-1}$which represent the stretching of (C=O) group respectively. These bands are shifted to 1573.54 cm$^{-1}$, 1748.48 cm$^{-1}$ and 1748.73 cm$^{-1}$ respectively. These results suggested that (CS/SA), (CS/XG) and (CS/CG) PECs were formed through the electrostatic interaction between the (-COO-) group in SA, XG and CG with (-NH$^{+}$) group in CS respectively.

Figure (1): FTIR spectra of (a)CS, (b)SA, (c) CS/SA PEC taken from the surface of the prepared tablets after sinking in 0.1 N HCl for 3 hrs and drying
Figure (3): FTIR spectra of (a) CS, (b) CG, (c) CS/CG PEC taken from the surface of the prepared tablets after sinking in 0.1 N HCl for 3 hrs and drying.

Flow Properties

The resulted values of angle of repose, Hausner’s ratio and Carr’s index for each formula before compression was given in table (2). The flowability of the formulas that contain the physical mixture of the polyelectrolytes (F1, F2, F3 and F7) showed the best results in comparison with other formulas. The improvement of flowability may be due to the reduction of the electrostatic charges of the polymers by the physical mixing of the polyelectrolytes [28].
**Table (2) Angle of Repose, Hausner’s ratio and Carr’s Index of the Physical Mixture Formulas**

<table>
<thead>
<tr>
<th>Formula No.</th>
<th>Angle of repose (degree)</th>
<th>Bulk density (g/cm³)</th>
<th>Tapped density (g/cm³)</th>
<th>Hausner’s ratio</th>
<th>Carr’s index (%)</th>
<th>Type of flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>29.00±0.00</td>
<td>0.475±0.02</td>
<td>0.516±0.04</td>
<td>1.08</td>
<td>7.94</td>
<td>Excellent</td>
</tr>
<tr>
<td>F2</td>
<td>26.33±1.52</td>
<td>0.477±0.01</td>
<td>0.517±0.02</td>
<td>1.08</td>
<td>7.73</td>
<td>Excellent</td>
</tr>
<tr>
<td>F3</td>
<td>25.33±0.57</td>
<td>0.479±0.01</td>
<td>0.519±0.01</td>
<td>1.08</td>
<td>7.70</td>
<td>Excellent</td>
</tr>
<tr>
<td>F4</td>
<td>30.66±0.57</td>
<td>0.461±0.01</td>
<td>0.519±0.02</td>
<td>1.12</td>
<td>11.17</td>
<td>Excellent</td>
</tr>
<tr>
<td>F5</td>
<td>35.33±0.57</td>
<td>0.445±0.01</td>
<td>0.507±0.02</td>
<td>1.13</td>
<td>12.22</td>
<td>Good</td>
</tr>
<tr>
<td>F6</td>
<td>40.00±1.00</td>
<td>0.420±0.02</td>
<td>0.508±0.01</td>
<td>1.20</td>
<td>17.32</td>
<td>Fair</td>
</tr>
<tr>
<td>F7</td>
<td>30.33±0.57</td>
<td>0.485±0.04</td>
<td>0.517±0.02</td>
<td>1.06</td>
<td>6.18</td>
<td>Excellent</td>
</tr>
<tr>
<td>F8</td>
<td>33.33±0.57</td>
<td>0.444±0.01</td>
<td>0.507±0.02</td>
<td>1.14</td>
<td>12.42</td>
<td>Good</td>
</tr>
<tr>
<td>F9</td>
<td>30.66±0.57</td>
<td>0.461±0.02</td>
<td>0.518±0.04</td>
<td>1.12</td>
<td>11.00</td>
<td>Excellent</td>
</tr>
<tr>
<td>F10</td>
<td>35.00±0.00</td>
<td>0.446±0.01</td>
<td>0.508±0.02</td>
<td>1.13</td>
<td>12.20</td>
<td>Good</td>
</tr>
</tbody>
</table>

**Hardness Test**

The results of hardness of naproxen sustained release tablet are given in table (4). The formulas F1 to F10 (except F7 and F8) that containing physical mixtures or as separate polymers have almost the same hardness values (8-9) kg/cm² since these formulas have the same amount of PVP, while F7 and F8 that contain CS/ XG physical mixture and XG respectively showed a higher values (11) kg/cm² may be due to the presence of xanthan gum which is one of the natural gums that can be applied in formulation of tablets as a binder because of its adhesive nature.[29].

**Friability Test**

The results of % friability of naproxen sustained release tablet is given in table (4). The acceptable percentage of weight loss should be less than 1% and was determined by the following equation[19]:

\[
F = \frac{\text{weight initial} - \text{weight final}}{\text{weight initial}} \times 100
\]

The % friability was less than 1% for all formulas.

**Weight Variation Test**

The results of weight variation test of naproxen sustained release tablets are showing in table (4). The requirements are met if no more than 2 tablets are outside the % limit and if there is no difference by double this percentage. The weight of each tablet in each formula was within the acceptable range according to USP table (3)[30][19].

**Table (3) Weight variation according to USP**

<table>
<thead>
<tr>
<th>Average weight of tablets(mg)</th>
<th>Percent deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>130mg or less</td>
<td>±10</td>
</tr>
<tr>
<td>More than 130mg and less than 324 mg</td>
<td>±7.5</td>
</tr>
<tr>
<td>324 mg or more</td>
<td>±5</td>
</tr>
</tbody>
</table>
### Table (4) Post Compression Parameters of Naproxen Sustained Release Tablet

<table>
<thead>
<tr>
<th>Formula No.</th>
<th>Hardness kg/cm²</th>
<th>Thickness mm</th>
<th>%Friability</th>
<th>Weight Variation mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>9.33±0.57</td>
<td>2.33±0.005</td>
<td>0.23±0.005</td>
<td>498.73±1.97</td>
</tr>
<tr>
<td>F2</td>
<td>8.83±0.28</td>
<td>2.12±0.015</td>
<td>0.24±0.015</td>
<td>499.79±2.58</td>
</tr>
<tr>
<td>F3</td>
<td>9.00±0.00</td>
<td>2.14±0.032</td>
<td>0.21±0.030</td>
<td>499.25±0.52</td>
</tr>
<tr>
<td>F4</td>
<td>9.33±0.57</td>
<td>2.62±0.036</td>
<td>0.22±0.017</td>
<td>497.90±0.42</td>
</tr>
<tr>
<td>F5</td>
<td>9.33±0.57</td>
<td>2.24±0.005</td>
<td>0.30±0.025</td>
<td>499.96±0.62</td>
</tr>
<tr>
<td>F6</td>
<td>8.33±0.57</td>
<td>2.33±0.005</td>
<td>0.47±0.026</td>
<td>495.60±0.52</td>
</tr>
<tr>
<td>F7</td>
<td>11.00±0.00</td>
<td>2.00±0.110</td>
<td>0.22±0.005</td>
<td>495.30±1.03</td>
</tr>
<tr>
<td>F8</td>
<td>11.83±0.28</td>
<td>2.11±0.005</td>
<td>0.26±0.005</td>
<td>498.46±0.95</td>
</tr>
<tr>
<td>F9</td>
<td>9.00±0.00</td>
<td>2.14±0.030</td>
<td>0.23±0.005</td>
<td>497.75±0.31</td>
</tr>
<tr>
<td>F10</td>
<td>8.43±0.51</td>
<td>2.36±0.030</td>
<td>0.43±0.005</td>
<td>498.12±0.33</td>
</tr>
</tbody>
</table>

### Drug Content

The total amount of naproxen was assayed only for formula F3, it was found that the drug content was 99.81% which corresponded to 249.52 mg of naproxen in 500 mg tablet. These results lie with acceptable range according to USP (the requirements are met if the amount of active ingredient in each dosage unit is not less than 95% and not more than 105% of the labeled amount).

### In Vitro Release Study Effect of the Formation of Polyelectrolyte Complex

The release of naproxen from formulas F3, F7 and F8 is shown in figure (4). Comparing between F3, F7 and F8, it was seen that after 7 hrs the release from F7 which contains 200mg SA was about 93.32% due to the presence of SA which is a pH sensitive polymer that forms a diffusion barrier on the surface of the tablet that leads to its swelling and erosion in the intestinal fluid and burst the release of the drug [9]. Whereas, the release of naproxen from F8 which contains 200mg CS was 72.21%, after 7 hrs due to the presence of CS which acts as a drug carrier and binder to extend the release of the drugs [31]. While in F3 which contains 150mg CSh + 50mg SA only 68.17% of naproxen was released after 7 hrs and the release was extended to 15 hrs, so the release was non significantly decreased(p>0.05), the reason behind that is the formation of PEC between CSh and SA through an electrostatic interaction between the protonated amine (NH3+) group in CS and the carboxylate (COO-) group of SA which solved the problem of pH dependency due to the formation of complex [32].
On the other hand, the release of naproxen from F7, F8 (figure 5) was almost the same in the first 5 hrs, but after 6 hrs the release was significantly decreased (p<0.05) in F7 which contains (150mg CSh+XG 50mg) as only 18.72% of naproxen was released during the first 6 hrs and the release was extended to give 94.66% of drug after 20 hrs because of interpolymer complexation as in F3 [32] [33].

The release of naproxen from F9 and F10 was almost similar in the first 6 hrs (figure 6), but after 7 hrs the release from F9 which contains mixture of (150mg CSh+CG 50mg) was significantly decreased (p<0.05) only 30.13% of naproxen was released after 7 hrs and the release was extended to 14 hrs due formation of PEC between the oppositely charged polymers, which increased the capability of controlling the release and reduced pH dependence [9].
Effect of polymer to polymer ratio

The effect of different ratios on the release of naproxen from formulas F1, F2, F3 and F4 is shown in figure (7). These formulas were prepared by mixing CSh and SA in different ratios (1:1, 1:2, 3:1 and 1:3) respectively.

It was seen that in vitro release of naproxen might be affected by physicochemical properties of CS and SA since they are pH-dependent. Comparing the release from F1 which contains CSh/SA in a ratio of 1:1 with F2 which contains CSh/SA in a ratio of 1:2 the release of naproxen was significantly increased (p<0.05) to increased amount of SA in F2 which caused swelling and erosion of the polymer in the intestinal fluid. While comparing between F3 which contains CSh/SA in a ratio of 3:1 and F4 which contains CSh/SA in a ratio of 1:3, F3 showed the slowest release due to increasing amount of CS in the matrix which increased the interaction between the two polymers due to form a closer network that lead to decrease in the diffusion of the drug outwards of the tablets. The same results were obtained when studying (CS/SA) PEC for trimetazidine hydrochloride when the release of this drug decreased with increasing the ratio of (CS/SA) from (1:6,1:1, 2:1,4:1)\textsuperscript{31,34}. 

Figure (6): The Effect of the Formation of (CSh/CG) PEC on the Cumulative Release of Naproxen at pH 1.2 for the first 2hr and at pH 6.8 at 37℃ (n=3)
Conclusion:
Naproxen can be formulated as oral sustained release matrix tablet, using simple physical mixture of cationic and anionic polymers to form PECs without the need of the addition of acetic acid and this added an advantage of being safe, simple and less time consuming. FTIR spectroscopy showed that PEC could be formed as a film on the surface of the tablet through the electrostatic interaction between (-COO-) group of anionic polymers (SA, XG and CG) and (-NH3+) of cationic polymer CS when the pH of the dissolution was 1.2. The PECs retarded the erosion and swelling of the matrix which extended the release of naproxen and the formula containing the physical mixture of CS/XG formed the strongest PEC. F3 which contains CSh/SA in a ratio of 3:1 showed the slowest release due to increasing amount of CS in the matrix which increased the interaction between the two polymers to form a closer network that lead to decrease in the diffusion of the drug outwards of the tablets.

References:
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