Controlled release of niflumic acid from native, pregelatinized and crosslinked corn starches matrix tablets

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Abstract
The present paper is devoted to the study of the non-steroidal anti-inflammatory niflumic acid (NA) release from dosage forms in simulated gastric and intestinal liquids (pH=1.2 and 6.8). New formulations (tablets) based on native, pregelatinized and cross-linked (DSA) corn starches were developed and tested. The proposed matrices were used in order to modify the NA release and especially to reduce its gastrointestinal side effect. The cross-linked matrix i.e. distarch adipate (DSA) was obtained by chemical modification of native starch using adipic acid/acetic anhydride. The different starches were characterized by different methods (FTIR, X-ray, swelling power). As well, the effects of the matrix and its concentration on the drug release from tablets were investigated. Finally different mathematical models i.e. zero and first order, Higuchi and Korsmeyer–Peppas models were tested in order to evaluate the release mechanism.

Keywords: niflumic acid, drug delivery systems, corn starch, crosslinking.

Introduction
Several aspects of drug delivery systems are developed including co-precipitates [1], cylindrical [2] or spherical [3-4] dosage forms, disks or tablets [5-7] and microspheres or microcapsules [8-10]. These formulations are based on polymeric biomaterials; non-degradable or biodegradable [11, 12]. Native starches have been largely used as traditional natural excipients for reliable formulations and the introduction of the modified starches offered new advances in the controlled release formulations.

Starch modifications include chemical substitution [13, 14], crosslinking [15, 16], pregelatinization [17, 18], and retrogradation [19-21]. For example, in Dumoulin and al's work [22], crosslinked starch was applied to excipients for controlled drug release. The drug release time was found to be affected by degree of crosslinking. The most commonly used crosslinking agents for starch are epichlorohydrin, sodium trimetaphosphate [23, 24], tetraethylene glycol diacrylate [25], acetic anhydride [26], adipic acid [27] and others. The present paper is devoted in one hand to the chemical modification of corn starch using adipic acid and acetic anhydride and its characterization. In the other hand, several tablets composed from niflumic acid (NA) as active agent and different starches i.e. native starch (NS), pregelatinized starch (PS) or distarch adipate (DSA) as matrixes are elaborated and tested. Different formulations based on NA, which is considered as a nonsteroidal anti-inflammatory drug with both analgesic and antipyretic activities, have been developed. For this purpose, tablets composed from ethylcellulose as matrix were tested in order to modify the drug release [28], bicontinuous sucrose ester microemulsion was elaborated and the relationship between the microstructure and the efficacy of the microemulsion as a drug carrier system was investigated [29]. Also, the complexation of niflumic acid with cyclodextrins was studied in order to enhance its solubility [30]. Furthermore, morpholinoalkyl ester prodrugs of niflumic acid were synthesized and evaluated in vitro and in vivo for their potential use for oral delivery [31]. So, the main objective of the present research is to modify and particularly to slow down the niflumic acid release in stomach using native and modified starches as carriers. The drug dissolution experiments were established in simulated gastric (pH=1.2) and also in intestinal (pH=6.8) media. Different parameters related to the formulation compositions’ were varied. The effects of the matrix and its concentration on the drug release were evaluated. Finally, different mathematical models were tested in order to elucidate the release mechanism of NA from these formulations.

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2. Materials and methods

2.1. Chemicals

Native and pregelatinized corn starches from Wacker Specialities (Germany), Niflumic acid from Synopharm society (Germany), adipic acid acetic and anhydride acetic from Biochem, the other chemicals are of analytical grade.

2.2. Preparation of acetylated adipate crosslinked corn starch (DSA)

Starch slurry was prepared by adding 6 g of dried corn starch to 13 mL of deionized water at room temperature in reaction vessel equipment (250mL). The pH was maintained between 9.0 and 9.5 using a 3% (w/w) aqueous NaOH solution. The slurry was heated to 35°C with a temperature controller and then 0.6 g of adipic acid anhydride acetic mixture (5/30) was added drop-wise. The temperature was maintained at 35°C for 2 h and then the pH was adjusted to 6.5 using diluted HCl (0.1 N).

The resulting starch suspension was vacuum-filtered through filter paper (Whatman 110 mm) and washed twice with 15mL of distilled water and once with ethanol. Finally, the recovered starch was dried in an oven at 45°C for 24 h. After a slight grinding, the dried starch was passed through a standard 100µm-mesh sieve.

The acetyl content was 3.566% and was determined according to the methods of Würzburg.[32]

2.3. Starch characterization

Fourier-transform infrared (FT-IR) spectroscopy

The IR spectra were obtained from samples in KBr pellets using Bruker FT-IR spectrophotometer (Germany).

Powder X-Ray diffraction analysis

The X-ray diffratograms were recorded by a copper anode X-ray tube using an analytical diffractometer (D8 Bruker Karlsruhe, Germany) operated at: 40 mA and 30 kV.

Swelling power of native and pregelatinized starches and distarch adipate (DSA)

Swelling power was determined using the method of Leach, McCowen, and Schoch.[33] Starch samples (0.025 g, dried base) were precisely weighed and transferred into clear dried test tubes and weighed with the test tubes (W1). 5 mL of distilled water was added to the test tube and mixed thoroughly with a Heidolph mixer for 30 s. The resultant slurries were then heated in water bath at selected temperatures; from 62°C to 74°C for native corn starch and from 64°C to 92°C for DSA and pregelatinized starch. Afterward the suspension was cooled rapidly to room temperature and centrifuged at 50rpm for 15min (Zentafugen Hettich). The weight of the residue (after decanting the supernatant) was obtained (W2).

The starch swelling (SP) was then calculated from the equation:

\[ SP = \frac{W_2 - W_1}{W_5} \] (1)

W1 is the weight of starch (dry matter basis).

2.4. Preparation of NA tablets

Nine formulations of NA with different percentages of matrix (native, pregelatinized starches and DSA) i.e. 10%, 20% and 30% were prepared as described below and reported in table1.

In one hand, 250mg of NA per tablet (50%) and only two thirds of total mass of native or pregelatinized or crosslinked starch are mixed in mortar. In the other hand, 20mg of PVP K30 as binder are dissolved in 0.8 mL of purified water. Then the solution is slowly poured on the last powder and the mixture is homogenized for 15 min.

A rest of starch and microcrystalline cellulose/lactose (70/30) as diluents were then added to the dried powder and the mixture is homogenized with 1% of magnesium stearate as lubricant. Tablets (500mg) with a diameter of 1.3 cm and width of 2.5 mm are prepared by compression under 12T/cm² of pressure and using laboratory press hydraulic (Shimadzu IR accessory, Japan).

2.5. In vitro tests of drug dissolution

Drug release kinetics from tablets were performed in a closed dissolution reactor, kept at a temperature of 37°C ±0.5°C with a controlled rate stirring (100 rpm) using paddle apparatus (Heidolph RZR 2041) for 120 min (the time corresponding to the drug stay in stomach) in pH = 1.2 and 360 min in pH = 6.8 (the time corresponding to the drug stay in jejunum). A tablet is plunged in 900mL of simulated gastric or intestinal liquid (pH=1.2, pH=6.8). Samples (4mL) of solution are taken at different intervals for analysis using a UV-spectrophotometer (SHIMADZU Model UV-1700, in pH = 1.2 at \( \lambda_{\text{max}} = 254 \) nm where \( \varepsilon = 463 \ \text{L} \cdot \text{g}^{-1} \cdot \text{cm}^{-1} \), in pH = 6.8 at \( \lambda_{\text{max}} = 286 \) nm where \( \varepsilon = 663 \ \text{L} \cdot \text{g}^{-1} \cdot \text{cm}^{-1} \),) after an appropriate dilution with pure buffer solutions (pH = 1.2 or pH = 6.8).
Table 1. Characteristics of the tested tablets

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Matrix</th>
<th>Matrix mass (mg)</th>
<th>MS mass (mg)</th>
<th>PVP K30 mass (mg)</th>
<th>MC/L mass (mg)</th>
<th>NA mass (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>NS</td>
<td>50</td>
<td>5</td>
<td>20</td>
<td>175</td>
<td>250</td>
</tr>
<tr>
<td>F2</td>
<td>NS</td>
<td>100</td>
<td>5</td>
<td>20</td>
<td>125</td>
<td>250</td>
</tr>
<tr>
<td>F3</td>
<td>NS</td>
<td>150</td>
<td>5</td>
<td>20</td>
<td>75</td>
<td>250</td>
</tr>
<tr>
<td>F4</td>
<td>PS</td>
<td>50</td>
<td>5</td>
<td>20</td>
<td>175</td>
<td>250</td>
</tr>
<tr>
<td>F5</td>
<td>PS</td>
<td>100</td>
<td>5</td>
<td>20</td>
<td>125</td>
<td>250</td>
</tr>
<tr>
<td>F6</td>
<td>PS</td>
<td>150</td>
<td>5</td>
<td>20</td>
<td>75</td>
<td>250</td>
</tr>
<tr>
<td>F7</td>
<td>DSA</td>
<td>50</td>
<td>5</td>
<td>20</td>
<td>175</td>
<td>250</td>
</tr>
<tr>
<td>F8</td>
<td>DSA</td>
<td>100</td>
<td>5</td>
<td>20</td>
<td>125</td>
<td>250</td>
</tr>
<tr>
<td>F9</td>
<td>DSA</td>
<td>150</td>
<td>5</td>
<td>20</td>
<td>75</td>
<td>250</td>
</tr>
</tbody>
</table>

*NS: native starch, PS: pregelatinized starch, DSA: distarch adipate, MS: magnesium stearate, MC/L: microcrystalline cellulose/lactose (70/30).

3. Results and discussion

3.1. Starches characterization

The comparison of the infrared spectra of native, pregelatinized and crosslinked (DSA) corn starches (see figure 1) showed clearly the appearance of the carbonyl (C=O) ester stretching vibration band at 1732cm⁻¹ in DSA spectrum. This band proved the successful cross-linking reaction (Scheme 1) of corn starch using adipate reagent (anhydride acetic and adipic acid).

![Scheme 1: chemical reaction of starch (St) cross-linking](image)

Concerning the swelling power values (SP), they were 7.28±0.48, 10.52±0.52 and 14.98±1.54 for respectively native, pregelatinized starch and distarch adipate (DSA). The results can be discussed on the base of both the presence of acetylene group and the cross-linking reaction. In fact, for DSA, the attraction between carbonyl group and water molecules may increase visibly the swelling rate of starch and also the cross-linking reaction creates more intra-molecular spaces in starch chains and so the inclusion of water molecules is favored.
In the X-ray diffractograms (figure 2), native starch showed strong reflection at $2\theta = 15^\circ$, 17°, 18° and 23° indicating a typical “A” type of starch [34]. Modification of starch did not cause any change in crystalline pattern. However, we remarked that the crosslinked starch (DSA) had low rate of cristallinity (43.5%) while the native starch had 47.8% of cristallinity. The results showed clearly that the adipic and acetyl groups caused a perturbation in structure of crystals. The pregelatinized starch diffractogram showed a large band at 19° indicating that the granules lost their semi-crystal structure.

![Figure 2: X-ray diffractograms of (A) native starch, (B) DSA and (C) pregelatinized starch.](image)

3.2. Drug dissolution

The drug release was tested in buffer solutions (pH=1.2 and 6.8), examples of NA release profiles are given in figures 3, 4, 5 and 6. The results showed that the in-vitro drug release from these tablets is influenced both by the nature of matrix (native, pregelatinized or crosslinked starches) (figures 3-6) and by the concentration of starch matrix in tablet as shown in figure 7. In fact, in one hand and regarding the type of starch, the percentage of drug released from F1 after 2 hours in acidic medium (pH=1.2) is 10.6% however it is 7.6% from F4 and it is the lower (4.8%) from F7; the same remark is noted when we compared F2, F5 and F8 and also for F3, F6 and F9, both in acidic or alkaline media. We concluded that whatever the matrix concentration in tablet (10, 20 or 30%), the drug transfer through the starch structure is more difficult when we used gelatinized or crosslinked starch matrices. The result is coherent because in gelatinized or cross-linked starch, the macromolecular chains are bind either by the water molecules as plasticizer or the cross-linking agent and so the mobility of NA became difficult. Then the drug release can be slow downed using these matrices.

In the other hand and regarding the matrix concentration, if we compared, for example, the dissolution profiles of F1 (10% of native starch), F2 (20%) and F3 (30%) (Figure 7) where the matrix was native starch, we remarked that the drug release is slow downed when we used a high percentage of starch (30%). Practically, the same effect is noted for the pregelatinized (F4, F5, F6) or cross-linked (F7, F8, F9) starch matrices as reported in table 2 where the percentage of drug released after 2 hours of matter transfer are displayed. Consequently, the drug release was the lower using 30% of distarch adipate (DSA) as matrix.

**Table 2.** Percentages of NA released after 2hours of drug release kinetics.

<table>
<thead>
<tr>
<th>Formulation</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>
</tr>
</thead>
<tbody>
<tr>
<td>pH=1.2</td>
<td>10.6</td>
<td>8.3</td>
<td>6.7</td>
<td>7.6</td>
<td>6.8</td>
<td>5.5</td>
<td>4.8</td>
<td>3.8</td>
<td>3.7</td>
</tr>
<tr>
<td>pH=6.8</td>
<td>16.1</td>
<td>14.2</td>
<td>13.1</td>
<td>13.0</td>
<td>12.6</td>
<td>12.1</td>
<td>10.9</td>
<td>10.4</td>
<td>9.5</td>
</tr>
</tbody>
</table>

Concerning the effect of the pH of release medium, the results showed that the niflumic acid is discharged rapidly in basic medium whatever the matrix’s nature or concentration. For example after 2 hours and from the formulation F7, 4.8% of drug was released in pH=1.2 (fig. 3), however at the same time 10.9% of drug was discharged in basic medium at pH=6.8 (fig. 5). The results are inevitably caused by the drug solubility in these
media; the results suited to our purpose since the drug release is slow in acidic medium (stomach) and then slightly speeded up in basic medium (intestine).

![Graph 1: Effect of native starch concentration (F1:10%, F2:20%, F3:30%) on the drug released (pH=1.2, T=37°C ±0.5°C).](image)

![Graph 2: Effect of starch matrix at 10% (F1: NS, F4: PS, F7: DSA) on the dissolution profiles (pH=1.2, T=37°C ±0.5°C).](image)

![Graph 3: Effect of starch matrix at 20% (F2: NS, F5: PS, F8: DSA) on the dissolution profiles (pH=1.2, T=37°C ±0.5°C).](image)

![Graph 4: Effect of starch matrix at 30% (F3: NS, F6: PS, F9: DSA) on the dissolution profiles (pH=1.2, T=37°C ±0.5°C).](image)

![Graph 5: Effect of starch matrix at 10% (F1:NS, F4: PS, F7: DSA) on the dissolution profiles (pH=6.8, T=37°C ±0.5°C).](image)

![Graph 6: Effect of starch matrix at 30% (F3: NS, F6: PS, F9: DSA) on the dissolution profiles (pH=6.8, T=37°C ±0.5°C).](image)

![Graph 7: Effect of native starch concentration (F1:10%, F2:20%, F3:30%) on the drug released (pH=1.2, T=37°C ±0.5°C).](image)

3.3. Data analysis
The release kinetics of NA were evaluated according to the following models for the earlier stage (2 hours of release time):
Zero order:
\[ Q_t = Q_0 + K_0 t \]  
(2)

First order
\[ \log(Q_t) = \log(Q_0) + K_1 t \]  
(3)

Higuchi model:
\[ Q_t = K_H(t)^{\frac{1}{2}} + a \]  
(4)

Korsmeyer–Peppas model:
\[ \frac{M_t}{M_i} = K_K(t)^n \]  
(5)

where \( Q_t \) (g/L) is the amount of drug dissolved in time \( t \) (min);
\( Q_0 \) is the initial amount of drug in the solution (most times \( Q_0 = 0 \));
\( M_t/M_i \) is the fractional drug release;
\( K_0, K_1, K_H \) and \( K_K \) are, respectively the zero order, the first order, the Higuchi’s and the Korsmeyer’s release constants; and \( n \) is an exponent which characterizes the drug release mechanism [35, 36].

The results of data analysis are regrouped in table 3 and 4. On the basis of the coefficient of correlation value, the mechanism of the drug release is discussed; in fact a model which gave a highest \( r^2 \) value is considered as the appropriate model. So, the most suitable kinetic models for describing the release of NA from the matrix tablets were Higuchi and/or Korsmeyer–Peppas models.

**Table 3.** Coefficients of correlation and release constants obtained from niflumic acid dissolution data analysis according to different mathematical models (pH=1.2).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi</th>
<th>Korsmeyer–Peppas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( K_0 \times 10^3 )</td>
<td>( r^2 )</td>
<td>( K_1 )</td>
<td>( r^2 )</td>
</tr>
<tr>
<td>F1</td>
<td>8.0</td>
<td>0.849</td>
<td>0.001</td>
<td>0.795</td>
</tr>
<tr>
<td>F2</td>
<td>1.2</td>
<td>0.957</td>
<td>0.004</td>
<td>0.873</td>
</tr>
<tr>
<td>F3</td>
<td>7.0</td>
<td>0.831</td>
<td>0.002</td>
<td>0.736</td>
</tr>
<tr>
<td>F4</td>
<td>11.0</td>
<td>0.958</td>
<td>0.004</td>
<td>0.907</td>
</tr>
<tr>
<td>F5</td>
<td>7.0</td>
<td>0.888</td>
<td>0.002</td>
<td>0.799</td>
</tr>
<tr>
<td>F6</td>
<td>6.0</td>
<td>0.962</td>
<td>0.002</td>
<td>0.910</td>
</tr>
<tr>
<td>F7</td>
<td>8.0</td>
<td>0.892</td>
<td>0.005</td>
<td>0.710</td>
</tr>
<tr>
<td>F8</td>
<td>6.0</td>
<td>0.849</td>
<td>0.004</td>
<td>0.709</td>
</tr>
<tr>
<td>F9</td>
<td>6.0</td>
<td>0.980</td>
<td>0.005</td>
<td>0.933</td>
</tr>
</tbody>
</table>

As a matter of fact, in the acidic medium, the matrix tablets (F1, F3) gave a highest coefficient of correlation \( (r^2) \) with Korsmeyer–Peppas model, the drug released from F4-7 corresponded to the Higuchi model however both the Higuchi and Korsmeyer–Peppas models are suitable for F2, F8 and F9 formulations (table 3). In basic medium, Korsmeyer–Peppas model was the appropriate model for most of formulations. Consequently and for all formulations, the release mechanism of niflumic acid is governed by the diffusion phenomenon and by applying the Korsmeyer–Peppas model the diffusion type is determined.

In fact, the \( n \) exponent from Korsmeyer–Peppas model can be used to characterize the drug release mechanisms as Fick diffusion, when \( n = 0.5 \) and as a non-Fickian model if \( n \) is higher than 0.5.
From the kinetic results, the exponent $n$ varied from 0.197 to 0.651 in pH=1.2 (table 3) and from 0.158 to 0.471 in pH=6.8 (table 4). We concluded that the drug release is governed by diffusion, in majority according to a quasi-Fickian mechanism.

In pH=1.2, the diffusion through the native and pregelatinized starch is quasi-Fickian since $n<0.5$, however for the distarch adipate the diffusion is anomalous (non-Fickian) since $n>0.5$, this means the co-existence of both diffusion and erosion phenomena. In pH = 6.8, the diffusion is quasi-Fickian type whatever the matrix since the $n$ exponent didn’t exceed 0.5.

Table 4. Coefficients of correlation and release constants obtained from niflumic acid dissolution data analysis according to different mathematical models (pH=6.8).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi</th>
<th>Korsmeyer–Peppas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$K_0 \times 10^5$</td>
<td>$r^2$</td>
<td>$K_1$</td>
<td>$r^2$</td>
</tr>
<tr>
<td>F1</td>
<td>15</td>
<td>0.784</td>
<td>0.002</td>
<td>0.736</td>
</tr>
<tr>
<td>F2</td>
<td>11</td>
<td>0.735</td>
<td>0.001</td>
<td>0.678</td>
</tr>
<tr>
<td>F3</td>
<td>10</td>
<td>0.651</td>
<td>0.001</td>
<td>0.622</td>
</tr>
<tr>
<td>F4</td>
<td>08</td>
<td>0.681</td>
<td>0.001</td>
<td>0.655</td>
</tr>
<tr>
<td>F5</td>
<td>08</td>
<td>0.684</td>
<td>0.001</td>
<td>0.657</td>
</tr>
<tr>
<td>F6</td>
<td>08</td>
<td>0.653</td>
<td>0.001</td>
<td>0.607</td>
</tr>
<tr>
<td>F7</td>
<td>14</td>
<td>0.935</td>
<td>0.003</td>
<td>0.870</td>
</tr>
<tr>
<td>F8</td>
<td>15</td>
<td>0.921</td>
<td>0.004</td>
<td>0.790</td>
</tr>
<tr>
<td>F9</td>
<td>14</td>
<td>0.960</td>
<td>0.004</td>
<td>0.847</td>
</tr>
</tbody>
</table>

Conclusion

In the present paper, new formulations based on native and cross-linked starches were developed in order to modify and slow down the niflumic acid release especially in acidic medium. The starches characterization demonstrated that the cross-linking reaction was successfully realized. The in-vitro experimental studies showed that the niflumic acid release can be slowed down either by using the distarch adipate as matrix or by increasing the starch concentration in tablet. The release kinetics are governed by diffusion and in general the Korsmeyer–Peppas model seemed that be the suitable model for describing the release process.

Acknowledgement - We wish to thank Salem pharmaceutical company (Algeria) for providing niflumic acid, native and pregelatinized corn starches.

References


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