FORMULATION AND EVALUATION OF DICLOFENAC CR TABLETS EMPLOYING CROSS LINKED STARCH UREA- A NEW MODIFIED STARCH

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ABSTRACT

Controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of the drug to a tissue. Drug release from these systems should be at a desired rate, predictable and reproducible. Polymers which are used as release-retarding materials in the design of controlled release drug delivery systems play a vital role in controlling the delivery of drug from the systems. Though a wide range of polymers and other release retarding polymers are available, there is a continued need to develop new and more efficient release retarding polymers for controlled release. The objective of the present study is to develop a new release – retarding and rate controlling polymer for controlled release. Starch-urea cross-linked with calcium, a new modified starch was synthesized and evaluated for its application in the formulation of controlled release tablets of diclofenac. Controlled release formulation is needed for diclofenac because of its short biological half life of 2.0 h, and also to minimize GI disturbances such as peptic ulceration with bleeding. Diclofenac (100 mg) matrix tablets were formulated employing starch urea and starch urea cross linked with calcium and were evaluated for drug release kinetics and mechanism.

Cross-linked starch-urea was more suitable than starch-urea for the design of controlled release tablets of diclofenac. Diclofenac release from the matrix tablets formulated employing cross-linked starch-urea was slow and spread over 24 h and depended on percent polymer in the tablets. A good linear relationship was observed between percent polymer in the tablets and release rate. Drug release from the matrix tablets formulated employing cross linked starch –urea was diffusion controlled and followed zero order kinetics. Non – Fickian diffusion was the drug release mechanism from the matrix tablets formulated employing starch-urea and cross linked starch-urea. Diclofenac release from the tablets formulated employing cross linked starch –urea (DF3) gave release over 24 h and similar to that from commercial diclofenac SR tablets. Diclofenac CR tablets for once-a-day (24 h) administration could be designed employing cross-linked starch-urea.

Key words: Cross linked starch urea, Diclofenac, Controlled release, Matrix tablets
INTRODUCTION

Controlled drug delivery is a topic of current interest in pharmaceutical technology and industry. Controlled release drug delivery systems are those formulations designed to release an active ingredient at rates, which differ significantly from their corresponding conventional dosage forms. The controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of therapeutic activity and / or targeting the delivery of the drug to a tissue. Drug release from these systems should be at a desired rate, predictable and reproducible. Polymers which are used as release-retarding materials in the design of Controlled release drug delivery systems play a vital role in controlling the delivery of drug from the systems. The success of Controlled drug delivery systems depends on how well the polymer regulates the release of drug from the system. Though a wide range of polymers and other release retarding polymers are available, there is a continued need to develop new and more efficient release retarding polymers for controlled release. A survey of the literature revealed that modified starches are promising and having good potential as release retardants and rate controlling polymers for controlled release. The controlled release properties of modified starches generally based on solvent-activation have been intensively investigated. For example, pre-gelatinized starch\(^1\), cross linked amylose\(^2\), substituted amylose\(^3\), short-chained amylose (i.e. amylodextrin)\(^4,5\) and calcium starch\(^6,7\), all have retarded drug release from matrix tablets.

The objective of the present study is to develop a new release – retarding and rate controlling polymer for controlled release. Starch-urea cross-linked with calcium, a new modified starch was synthesized, and evaluated for its application in controlled release. Starch reacts with urea to form starch carbamate, a starch urea polymer. Khalil \textit{et al.}\(^8\) investigated the reactions between starch and urea resulting in the formation of starch – urea polymer. No reports are available on the pharmaceutical applications of starch urea.

Among the various approaches, preparation of drug embedded matrix tablets is one of the least complicated techniques for controlled release and is widely used in industry. This technique was selected for the design of controlled release drug delivery systems employing starch urea and starch urea cross–linked with calcium. Diclofenac, a widely prescribed anti-inflammatory and analgesic drug, which requires controlled release formulation is included in the study.
to develop its controlled release formulations employing starch urea and cross-linked starch urea. Diclofenac sodium is a widely used non-steroidal anti-inflammatory analgesic and anti-pyretic drug. Controlled release formulation is needed for diclofenac because of its short biological half life of 2.0 h. The drug also causes gastro intestinal disturbances, peptic ulceration with bleeding if present in large concentration in gastrointestinal tract. Hence, diclofenac is a suitable drug for oral sustained and controlled release and it would be advantageous to slow down its release in gastrointestinal tract not only to prolong its therapeutic action but also to minimize possible side effects of diclofenac.

**EXPERIMENTAL**

**Materials:**

Diclofenac was a gift sample from M/s Micro labs Ltd, Pondicherry. Sodium hydroxide (Qualigens), Potassium dihydrogen orthophosphate (Qualigens) Talc I.P. (Loba Chemie), Magnesium stearate I.P. (Loba Chemie), Potato starch (Loba Chemie), Urea (Qualigens) and Calcium chloride I.P were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

**Methods:**

**Preparation of starch urea**:土豆 starch (9 parts) was dispersed in purified water (10 parts) to form starch slurry. Urea (1 part) was dissolved in purified water (40 parts) and the solution was heated to boiling. While boiling, the starch slurry was added and mixed. Mixing while heating was continued for 20 minutes to form starch-urea polymer. The mass formed was spread on to a stainless steel plate and dried at $85^\circ C$ for 6-8 h. The dried polymer was powdered and passed through mesh No. 120.

**Preparation of cross linked starch urea polymer**:土豆 starch (9 parts) was dispersed in purified water (10 parts) to form starch slurry. Urea (1 part), calcium chloride (1 part) were dissolved in purified water (40 parts) and the solution was heated to boiling. While boiling, the starch slurry was added and mixed. Mixing while heating was continued for 20 minutes to form cross-linked starch-urea polymer. The mass formed was spread on to a stainless steel plate and dried at $85^\circ C$ for 6-8 h. The dried polymer was powdered and passed through mesh No. 120.
Preparation of tablets:

Matrix tablets of diclofenac (100 mg) were prepared employing (i) starch-urea (ii) cross-linked starch-urea in different proportions of drug and polymer as per the formulae given in Table 1. The required quantities of medicament and matrix materials were mixed thoroughly in a mortar by following geometric dilution technique. The binder, water-alcohol (1:1) solution was added and mixed thoroughly to form dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60°C for 4 h. The dried granules were passed through mesh No. 16 to break aggregates. The lubricants talc (2%) and magnesium stearate (2%) were passed through mesh No. 100 on to dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a rotary multi-station punching machine (Cadmach Machinery Co. Pvt. Ltd., Mumbai) to a hardness of 8-9.5 kg/sq.cm. using 9 mm round and flat punches.

Estimation of diclofenac in tablets:

Five tablets were accurately weighed and powdered. Tablet powder equivalent to 25 mg of medicament was taken into 25ml volumetric flask and 20 ml of methanol were added. The mixture was shaken thoroughly for about 30 min. while warming in hot water bath to dissolve the diclofenac. The solution was then made upto volume with methanol. The methanolic solution was subsequently diluted suitably with phosphate buffer of pH 7.4 and assayed for diclofenac at 276 nm. Four samples of tablet powder were analyzed in each case.

Evaluation of tablets:

Hardness:

Hardness of the matrix tablets prepared was tested using a Monsanto Hardness Tester.

Friability:

Friability of the matrix tablets prepared was determined in a Roche Friabilator.

Disintegration time:

Disintegration times were determined in Thermonic Tablet Disintegration Test Machine using 0.1 N hydrochloric acid, distilled water and phosphate buffer of pH 7.4 as fluids.

Drug release study:

Drug release from the matrix tablets prepared was studied using 8 station dissolution rate test apparatus (Lab India, Disso 2000) employing a paddle stirrer at 50 rpm and at 37± 0.5°C. Phosphate buffer of pH 7.4 (900ml) was used as dissolution fluid. Samples of 5 ml of each were withdrawn at different time intervals over a
period of 24 h. Each sample withdrawn was replaced with an equal amount of fresh dissolution medium. Samples were suitably diluted and assayed at 276 nm for diclofenac using an Elico BL 198 double beam UV-spectrophotometer. For comparison, drug release from Reactin SR tablets (a commercial Diclofenac SR product) was also studied. The drug release experiments were conducted in triplicate in each case.

Data analysis:

Release data were analyzed as per zero order, first order, Higuchi\textsuperscript{11} and Korsmayer-Peppas\textsuperscript{12} equation models to assess the drug release kinetics and mechanism from the matrix tablets prepared.

RESULTS AND DISCUSSION

Matrix tablets of Diclofenac (100 mg) could be prepared employing (i) starch-urea (ii) cross-linked starch-urea in different proportions (33, 50, and 66 strengths in the formulae) by wet granulation method as per the formulae given Table 1.

<table>
<thead>
<tr>
<th>Formulation of Diclofenac Matrix Tablets Prepared Employing Starch-Urea and Cross Linked Starch-Urea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingredient (mg/tablet)</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Diclofenac</td>
</tr>
<tr>
<td>Starch-urea</td>
</tr>
<tr>
<td>Cross-linked-Starch urea</td>
</tr>
<tr>
<td>Talc</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
</tr>
<tr>
<td>Water- Alcohol (1:1)</td>
</tr>
<tr>
<td>Weight of the Tablet(mg)</td>
</tr>
</tbody>
</table>
The drug content and physical properties of the matrix tablets prepared are given in Table 2. Hardness of the tablets was in the range of 8-8.5 kg/sq.cm. Weight loss in the friability test was less than 0.34 % in all the cases. All the matrix tablets prepared contained 100±3% of the labeled claim. All the tablets were found to be non-disintegrating in water, aqueous, acidic (pH 1.2) and alkaline (pH 7.4) fluids. As such, the prepared matrix tablets of diclofenac were of good quality with regard to drug content, hardness and friability. As the tablets formulated employing starch-urea and cross-linked starch-urea were non-disintegrating in acidic and alkaline fluids, they are considered suitable for oral controlled release.

Table 2

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Hardness (kg/Sq.cm)</th>
<th>Friability (%)</th>
<th>Disintegration-Time</th>
<th>Diclofenac Content (mg/tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DF1</td>
<td>8.0</td>
<td>0.30</td>
<td>Non Disintegrating</td>
<td>102.30±12</td>
</tr>
<tr>
<td>DF2</td>
<td>8.5</td>
<td>0.10</td>
<td>Non Disintegrating</td>
<td>101.05±0.8</td>
</tr>
<tr>
<td>DF3</td>
<td>8.0</td>
<td>0.20</td>
<td>Non Disintegrating</td>
<td>100.13±0.6</td>
</tr>
<tr>
<td>DF4</td>
<td>8.5</td>
<td>0.20</td>
<td>Non Disintegrating</td>
<td>98.52±1.4</td>
</tr>
<tr>
<td>Reactin SR</td>
<td>8.5</td>
<td>0.34</td>
<td>Non Disintegrating</td>
<td>101.40±1.1</td>
</tr>
</tbody>
</table>
Diclofenac release from the matrix tablets prepared was studied in phosphate buffer of pH 7.4. Drug release profiles of diclofenac matrix tablets prepared and commercial SR formulation are shown in Fig. 1. The drug release parameters are summarized in Table 3.

Table 3
Diclofenac Release Characteristics of Matrix Tablets Formulated Employing Starch Urea, Cross Linked Starch-Urea and Commercial

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Polymer and its Concentration (%)</th>
<th>T50 (h)</th>
<th>T90 (h)</th>
<th>K0 (mg/h)</th>
<th>K1 (h⁻¹)</th>
<th>n’ in Peppas equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>DF1</td>
<td>SU (50%)</td>
<td>1.7</td>
<td>3.58</td>
<td>21.77</td>
<td>0.8235</td>
<td>0.835</td>
</tr>
<tr>
<td>DF2</td>
<td>CSU (33%)</td>
<td>4.05</td>
<td>8.25</td>
<td>9.26</td>
<td>0.306</td>
<td>0.635</td>
</tr>
<tr>
<td>DF3</td>
<td>CSU (50%)</td>
<td>6.15</td>
<td>15.0</td>
<td>5.708</td>
<td>0.221</td>
<td>0.588</td>
</tr>
<tr>
<td>DF4</td>
<td>CSU (66%)</td>
<td>9.0</td>
<td>20.15</td>
<td>4.58</td>
<td>0.153</td>
<td>0.736</td>
</tr>
<tr>
<td>Reactin SR tablets</td>
<td>---</td>
<td>6.0</td>
<td>16.8</td>
<td>4.09</td>
<td>0.1841</td>
<td>0.573</td>
</tr>
</tbody>
</table>
Diclofenac release from the prepared matrix tablets was slow and spread over 24 h and depended on the polymer type and concentration of cross linked starch-urea polymer in the tablets.

Diclofenac release was relatively rapid in the case of matrix tablets prepared employing starch-urea polymer at 50% strength and the release was complete in 5 h. Whereas when cross-linked starch-urea polymer was used at the same strength of 50% in the formula, the release was much slow and spread over 24 h. As the concentration of cross-linked starch-urea polymer in the matrix tablets was increased, the release rate was decreased. A good linear relationship was observed between percent polymer in the tablets and release rate (K₀ or K₁). The relationship could be expressed by the linear equation, $y = -0.142x + 13.59$ ($r^2 = 0.9272$) where X is the polymer strength (%) and Y is release rate, K₀ (mg/h).

The drug release data were analyzed as per Zero order, First order, Higuchi, and Korsmayer- Peppas equation models. Analysis of release data as per zero order and first order kinetic models indicated that the drug release followed zero order kinetics. Correlation coefficient (r) values were relatively higher in zero order model than those in first order model with all the prepared tablets. Plots of percent release versus square root of time were found to be linear with $r > 0.9523$ with all the tablets prepared indicating that the drug release from these tablets was diffusion controlled. When the release data were analyzed as per Korsmayer-Peppas equation, the release exponent ‘n’ was in the range 0.588 - 0.835 indicating non - Fickian (anomalous) diffusion as the release mechanism from all the tablets prepared with starch- urea and cross-linked starch-urea.

For comparison, diclofenac release from one commercial SR brand (Reactin SR tablets) was also studied. A comparison of the drug release profiles of formulated matrix tablets and commercial SR product revealed that the release profile of formulation DF3 was comparable to that of commercial SR product (Reactin SR tablets). Drug release profiles of formulation DF3 and Reactin SR tablets were compared by calculating difference factor $f_1$ and similarity
factor $f_2$. A value of $f_1 < 15$ and $f_2 > 50$ indicate similarity of the two drug release profiles. The values of $f_1$ and $f_2$ were found to be 3.16 and 76.73 respectively for the comparison of release profiles of formulation DF3 and Reactin SR tablets indicating that the release profiles of these two products are similar. Hence, matrix tablets formulated employing cross-linked starch-urea (DF3) are considered suitable for controlled release of diclofenac over 24 h (i.e. once-a-day administration).

CONCLUSION

Cross-linked starch-urea was more suitable than starch-urea for the design of controlled release tablets of diclofenac. Diclofenac release from the matrix tablets formulated employing cross-linked starch-urea was slow and spread over 24 h and depended on percent polymer in the tablets. A good linear relationship was observed between percent polymer in the tablets and release rate. Drug release from the matrix tablets formulated employing cross linked starch –urea was diffusion controlled and followed zero order kinetics. Non – Fickian diffusion was the drug release mechanism from the matrix tablets formulated employing starch-urea and cross linked starch-urea. Diclofenac release from the tablets formulated employing cross linked starch –urea (DF3) gave release over 24 h and similar to that from commercial diclofenac SR tablets. Diclofenac CR tablets for once-a-day (24 h) administration could be designed employing cross-linked starch-urea.

REFERENCES


