FORMULATION AND EVALUATION OF DICLOFENAC SODIUM SUSTAINED RELEASE TABLETS USING SEED POWDER OF STRYCHNOS POTATORUM

Ramadevi K*, Padmavathi K, Sravani N, Chandra Sekhara Rao G

Department of Pharmaceutical Technology, Yalamarty Pharmacy College, Visakhapatnam, Andhra Pradesh, India.

ABSTRACT

Sustained release drug delivery systems are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. The success of sustained drug delivery system depends on how well the polymer regulates the release of drug from the systems. Though a wide range of release retarding polymers are available, there is a continued need to develop new and more efficient release-retarding polymers for sustained release. The use of natural polymers for pharmaceutical applications is attractive because they are economical, readily available, non-toxic and biodegradable. The present work was aimed at evaluating the sustained release properties of seed powder of medicinal plant Strychnos potatorum. Diclofenac sodium was used as model drug. Matrix tablets were prepared by wet granulation technique and evaluated for friability, drug content and in vitro drug release. It can be concluded that seed powder of Strychnos potatorum can be used as a promising release retardant polymer in the formulation of sustained release dosage forms.

Key words: Sustained release drug delivery systems, Seed powder, Diclofenac sodium.

INTRODUCTION

Sustained release drug delivery systems are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of injectable dosage forms, this period may vary from days to months. In the case of orally administered forms, this period is measured in hours (Leon Lachman et al., 2009). Two general sets of methods have been developed for implementation of practical sustained release dosage form designs: approaches based on drug modification and approaches based on dosage form modification. Two general principles are involved in retarding drug release from sustained release formulations: embedded matrix (drug is dispersed in matrix of retardant material) and barrier principle (layer of retardant material between drug and elution medium).

Polymers, which are used as release-retarding materials in the design of sustained release drug delivery systems, play a vital role in controlling the delivery of drug from the systems. The success of sustained drug delivery system depends on how well the polymer regulates the release of drug from the systems. Though a wide range of release retarding polymers are available, there is a continued need to develop new and more efficient release-retarding polymers for sustained release. The use of natural polymers for pharmaceutical applications is attractive because they are economical, readily available, non-toxic and biodegradable. Many plant products such as mucilage of Hibiscus rosa-sinensis (Pawan P et al., 2013), Oryza sativa hull powder (Thube R et al., 2012), cashew nut tree gum (Ganesh GNK et al., 2010), gum from tamarind seed (Malviya R et al., 2010), juice of...
Citrus limetta (Pawan Guar K et al., 2012) were used as release retardant polymers in formulation of sustained release tablets. The present work was aimed at evaluating the sustained release properties of seed powder of medicinal plant Strychnos potatorum. Some earlier works also reported the seed powder as an emulsifying agent (Chandra Sekhara Rao G et al., 2011).

Diclofenac sodium was used as model drug. Diclofenac sodium is a nonsteroidal anti-inflammatory agent used for a variety of painful and inflammatory conditions. It has a short biological half-life of 1–2 hours. Therefore this drug is an ideal candidate for developing sustained release dosage forms.

MATERIALS AND METHODS

Diclofenac sodium was purchased from Yarrow Chem Products, Mumbai. Seed powder was collected from Strychnos potatorum purchased in local market. Lactose from Fischer Scientific India Pvt. Ltd., Mumbai, Magnesium stearate from Qualikems Fine Chemicals Pvt. Ltd., New Delhi and Talc from Kemphasol, Mumbai were purchased. All other chemicals were of analytical grade.

Milling of Seeds of Strychnos potatorum

The seeds of Strychnos potatorum Linn. Family Loganiaceae were collected, authenticated and specimen was preserved in herbarium by Professor Venkayya, Department of Botany, Andhra University, Visakhapatnam. The seeds were dried in oven at 40°C for 12 hrs and converted into a powder by using mixer grinder. The powder was passed through sieve no. 100. The collected powder was stored in a dessicator.

Evaluation of Flow Properties of Seed Powder

The flow ability of the powder was determined by angle of repose, Bulk Density (BD), Tapped Density (TD), Carr’s Index (CI), and Hausner’s ratio parameters.

Angle of Repose

The angle of repose of seed powder was determined by the fixed funnel method. Accurately weighed seed powder was taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder. The powder was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

\[ \tan \theta = \frac{h}{r} \]

Where, \( h \) = height of the powder cone, \( r \) = radius of the powder cone.

Bulk Density (BD) & Tapped Density (TD)

A quantity of powder was introduced into 10 ml measuring cylinder. The initial volume was noted. The cylinder was allowed to fall under its own weight. Tapping was continued until no further change in volume was noted (Excel Enterprises, Kolkata).

Bulk density = mass of powder / bulk volume

Tapped density = mass of powder / tapped volume

Carr’s Index (CI)

The percentage compressibility of a powder (Carr’s index) is calculated by the formula

\[ CI (\%) = \frac{(TD – BD) * 100}{TD} \]

Hausner Ratio

The Hausner ratio is calculated by the formula

\[ Hausner Ratio = \frac{TD}{BD} \]

Preparation of Sustained Release Matrix Tablets

Matrix tablets containing Diclofenac sodium were prepared by wet granulation technique using variable concentrations of seed powder. Required quantity of drug, seed powder and lactose were mixed thoroughly. Purified water was added slowly to the above mixture with uniform mixing to get a wet mass. The wet mass was passed through sieve no. 14 to obtain granules. The granules were dried at 75°C for 30 minutes. The dried granules were passed through sieve no.16. Talc and magnesium stearate were added to the dried granules and mixed thoroughly. Finally, the granules were compressed into tablets using 9 mm flat faced punches of rotary tablet compression machine (Shakti).

Evaluation of Tablets

Thickness (Leon Lachman et al., 2009)

The thickness of tablets was determined by using Screw Gauge. Thickness of five tablets from each formulation was determined and the average value was calculated.

Limit: Tablet thickness should be controlled within a ±5% variation of a standard value.

Hardness (Leon Lachman et al., 2009)

The hardness of tablets was determined by using Monsanto hardness tester (Inco, Ambala). Hardness of five tablets from each formulation was determined and the average value was calculated.

Uniformity of Weight (IP, 2007)

To study weight variation, each 20 tablets were selected randomly from all formulations. Each tablet was weighed individually and average weight was calculated.

IP Limit: NMT two of the individual weights deviate from average weight by more than 5% and none deviates by more than twice that percentage.

Friability (IP, 2007)

Required number of tablets were weighed and placed in drum (Roche friabilator). The friabilator was operated at 25rpm for 4 minutes. The tablets were
removed of any loose dust from them and weighed again. The friability was calculated.

**IP Limit**: A maximum loss of weight not greater than 1% is acceptable.

**Drug content** (Puranaik MP *et al.*, 2005)  
Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in 0.1N sodium hydroxide, the drug content was determined measuring the absorbance at 276 nm after suitable dilution using UV-Vis double beam spectrophotometer (Elico, SL 159).

**In Vitro Dissolution Studies** (Puranaik MP *et al.*, 2005)  
The *in vitro* release of Diclofenac sodium from the formulated tablets was carried out in tablet dissolution apparatus (Electro Lab TDT - 08L) using 900 ml of dissolution medium maintained at 37.0 ±0.5°C and a stirring rate of 50 rpm. Three tablets from each formulation were tested individually in simulated gastric fluid (0.1N HCl) for the first 2 hours and in phosphate buffer pH 7.4 for the following 10 h. At every 1 h interval, samples of 5 ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the amount of DS present in each sample was determined spectrophotometrically at 276 nm and cumulative percentage drug release was calculated.

**Kinetics of Drug Release**  
To examine the drug release kinetics, the cumulative release data were fitted to models representing zero order \(Q \text{ v/s } t\) and first order \(\log(Q_0 - Q) \text{ v/s } t\), where \(Q\) is the cumulative percentage of drug released at time \(t\) and \((Q_0 - Q)\) is the cumulative percentage of drug remaining after time \(t\).

**RESULTS**

**Table 1. Composition of Sustained Release Tablets**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1 (mg)</th>
<th>F2 (mg)</th>
<th>F3 (mg)</th>
<th>F4 (mg)</th>
<th>F5 (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac Sodium</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Seed Powder of <em>Strychnos potatorum</em></td>
<td>60</td>
<td>90</td>
<td>120</td>
<td>150</td>
<td>180</td>
</tr>
<tr>
<td>(20%)</td>
<td>(30%)</td>
<td>(40%)</td>
<td>(50%)</td>
<td>(60%)</td>
<td></td>
</tr>
<tr>
<td>Lactose</td>
<td>131</td>
<td>101</td>
<td>71</td>
<td>41</td>
<td>11</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Talc</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Purified Water</td>
<td>qs</td>
<td>qs</td>
<td>qs</td>
<td>qs</td>
<td>qs</td>
</tr>
<tr>
<td>Total Weight</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
</tr>
</tbody>
</table>

**Table 2. Flow Properties of Seed Powder of *Strychnos potatorum***

<table>
<thead>
<tr>
<th>Angle of Repose</th>
<th>48.48°</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk Density</td>
<td>0.45mg/ml</td>
</tr>
<tr>
<td>Carr’s Index</td>
<td>30.56%</td>
</tr>
<tr>
<td>Hausner’s Ratio</td>
<td>1.44</td>
</tr>
</tbody>
</table>

**Table 3. Evaluation of Tablets**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Thickness (mm)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Weight variation (mg)</th>
<th>Drug content (%) (mean ± sd, n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>4.66</td>
<td>6.0</td>
<td>0.16</td>
<td>290.1±3.2%</td>
<td>95.4±0.28</td>
</tr>
<tr>
<td>F2</td>
<td>4.7</td>
<td>6.0</td>
<td>0.33</td>
<td>297.0±2.4%</td>
<td>97.0±0.21</td>
</tr>
<tr>
<td>F3</td>
<td>4.69</td>
<td>5.5</td>
<td>0.17</td>
<td>302.5±1.3%</td>
<td>98.4±0.48</td>
</tr>
<tr>
<td>F4</td>
<td>4.79</td>
<td>4.5</td>
<td>0.06</td>
<td>296.2±1.7%</td>
<td>98.3±0.39</td>
</tr>
<tr>
<td>F5</td>
<td>4.7</td>
<td>3.0</td>
<td>0.20</td>
<td>291.0±3.1%</td>
<td>96.2±0.14</td>
</tr>
</tbody>
</table>

**Table 4. Cumulative Percentage of Drug Released from Tablets** (mean ± sd, n = 3)

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42.6±0.17</td>
<td>36.7±0.16</td>
<td>30±0.04</td>
<td>24.2±0.10</td>
<td>22.1±0.08</td>
</tr>
<tr>
<td>2</td>
<td>61.6±0.12</td>
<td>50.3±0.23</td>
<td>39.0±0.2</td>
<td>31.6±0.04</td>
<td>29.7±0.06</td>
</tr>
<tr>
<td>3</td>
<td>72.4±0.05</td>
<td>60.1±0.32</td>
<td>58±0.11</td>
<td>39.7±0.2</td>
<td>32.1±0.15</td>
</tr>
<tr>
<td>4</td>
<td>85.8±0.13</td>
<td>69±0.55</td>
<td>69.5±0.3</td>
<td>48.4±0.13</td>
<td>47.5±0.23</td>
</tr>
<tr>
<td>5</td>
<td>92.6±0.21</td>
<td>77±0.14</td>
<td>75±0.36</td>
<td>55±0.28</td>
<td>53.1±0.22</td>
</tr>
<tr>
<td>6</td>
<td>98.7±0.16</td>
<td>87±0.08</td>
<td>78.8±0.32</td>
<td>60.8±0.11</td>
<td>58.2±0.2</td>
</tr>
</tbody>
</table>
Table 5. Correlation Coefficient values

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Zero Order model</th>
<th>First Order model</th>
<th>Higuchi model</th>
<th>Korsmeyer model</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.885</td>
<td>0.917</td>
<td>0.996</td>
<td>0.995</td>
<td>0.472</td>
</tr>
<tr>
<td>F2</td>
<td>0.904</td>
<td>0.910</td>
<td>0.998</td>
<td>0.998</td>
<td>0.471</td>
</tr>
<tr>
<td>F3</td>
<td>0.882</td>
<td>0.962</td>
<td>0.985</td>
<td>0.972</td>
<td>0.521</td>
</tr>
<tr>
<td>F4</td>
<td>0.958</td>
<td>0.97</td>
<td>0.988</td>
<td>0.989</td>
<td>0.561</td>
</tr>
<tr>
<td>F5</td>
<td>0.922</td>
<td>0.98</td>
<td>0.984</td>
<td>0.97</td>
<td>0.546</td>
</tr>
</tbody>
</table>

Fig 1. Zero Order Plots of Drug Released from Formulations

Fig 2. First Order Plots of Drug Released from Formulations

Fig 3. Higuchi Plots of Drug Released from Formulations

Fig 4. Korsmeyer-Peppas Plots of Drug Released from Formulations

DISCUSSION

In the present work, an attempt has been made to prepare sustained release matrix tablets of Diclofenac sodium using natural polymer namely seed powder of *Strychnos potatorum*.

Milling of Seeds of *Strychnos potatorum*

A fine brown colored powder was obtained with good flavor. The seeds do not show any toxic effects and phytochemical studies show the presence of carbohydrates, alkaloids, and saponins (Sanmugapriya E *et al.*, 2006).

Evaluation of Flow Properties of Seed Powder

The flow properties of seed powder were reported in Table No. 2. The values of angle of repose, Carr’s index and Hausner’s ratio indicate poor flow property of seed powder (Aulton ME, 2007).

Evaluation of Tablets

The thickness of tablets was about 4.66 mm to 4.79 mm (Table No. 3). The hardness of tablets was found to be in the range of 3 to 6 kg/cm². It was observed that with increase in concentration of seed powder, the
hardness of the tablets reduced. The % weight loss in friability test was found to be less than 1 (0.06% to 0.33%). The weight variation test for all the formulations was found to be within IP limits. Drug content of all formulations was found to be more than 95% and within the limits.

**In vitro Dissolution Studies**

As the drug is insoluble in 0.1N HCl, cumulative percentage drug release was insignificant in simulated gastric fluid in the first 2 hours. So, only drug release data of phosphate buffer was given in Table No. – 4. When the tablets were placed in phosphate buffer, initially swelling of the tablets was observed followed by gradual erosion of tablet matrix. In formulations F1 and F2, the drug release was rapid and completed within 6 & 8 hrs respectively. In formulations F4 and F5, the drug release was very slow and total drug was not released within 10 hrs. Formulation F3 was considered as optimum because the drug release was sustained and complete within 10 hrs.

**Kinetics of Drug Release**

The in vitro drug release data was evaluated kinetically by zero order, first order, Higuchi and Korsmeyer models (Figure No. – 1 to 4). The correlation coefficient values were found to be higher for first order kinetics when compared to zero order kinetics, indicating that the drug release follows first order kinetics. Higuchi plots were found to be linear in all formulations, indicating that the drug release was by diffusion mechanism. The release exponent ‘n’ as per Korsmeyer was in the range of 0.471 – 0.561, indicating non-Fickian (anomalous) diffusion as the release mechanism (Table No. – 5).

**CONCLUSION**

Results of the present study indicate that the natural substance, namely the seed powder of *Strychnos potatorum* can be employed as a release retardant material in the formulation of sustained release matrix tablets of diclofenac sodium. Seed powder of *Strychnos potatorum* produced diclofenac sodium tablets of sufficient strength and hardness. It was evident that the seed powder when used at a concentration of 40% was capable of sustaining the release of drug up to 10 hrs. Further, purification of seed powder may improve its release retardant properties. Further studies have been planned in this direction to establish the utility of this natural substance as a pharmaceutical excipient.

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