Preparation and Evaluation of Silymarin Controlled Release Tablets Prepared Using Natural Gums

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ABSTRACT: The aim of the study was to formulate and evaluate silymarin controlled release (CR) tablets using natural polymers (xanthan gum and guar gum) CR Tablets of silymarin were prepared by direct compression method at different ratios of 1:0.25, 1:0.5 and 1:0.75 (drug:polymers). The powder blend was evaluated for angle of repose, bulk density, tapped density, compressibility index and Hausner ratio. The powder blend showed satisfactory flow properties. The silymarin tablets are evaluated for general appearance, hardness test, friability test, weight variation and drug content estimation. All the tablets passed the tests. The interactions between the drug with highest proportion of polymers were determined by using FTIR studies. The FTIR study reveals that there is no interaction between drug and polymers. The invitro release study was carried out using 900ml of phosphate buffer pH 7.4 for 10 hours using USP type II dissolution apparatus. The results of invitro release studies of CR tablets of silymarin were compared with control (without polymer).

KEYWORDS: Silymarin; Xanthan gum; Guar gum; Controlled release; Direct compression

Introduction

During the past few decades, various types of oral controlled release (CR) formulations have been developed to improve the clinical efficacy of drugs having short half life and to increase the patient compliance. These formulations are designed to deliver drugs at a predetermined rate over a wide range of conditions (Aulton and Wells, 1988). The goal of designing controlled release drug delivery system (CRDDS) is to reduce the frequency of dosing and to improve the oral bioavailability of the drug. Various polymers are used to control the release of drugs from the dosage forms for absorption by the body (British Pharmacopoeia, 2000).

In the present investigation, studies were undertaken to formulate and evaluate oral CRDDS of silymarin widely used in the treatment of hepatoprotective, hepatoregenerative and antialhepatotoxic. It is freely soluble in methanol. It has elimination half-life of approximately 6 hours (Ganesh et al., 2008; Manekar et al., 1999). Based on these physico-chemical and bio-pharmaceutical properties, silymarin was selected as a drug candidate for developing CR tablet formulation.

The controlled release tablets can be prepared by direct compression method. Many polymers can be used in the formulation of CR drug delivery system. Xanthan gum and Guar gum is the best natural polymer, which has a wide application in formulating controlled release tablets.

The purpose of the study was the development of silymarin CR tablets by direct compression method and their Invitro evaluation.

Materials

Silymarin was obtained from Micro Laboratories Ltd., (Hosur) India. Xanthan gum and Guar gum were obtained from Loba Chemicals Pvt Ltd., Mumbai. All other chemicals and reagents used were of analytical grade.

Methods

Preparation of Tablets

Six formulations of CR tablets of silymarin using xanthan gum and guar gum with three different ratios such as (1:0.25, 1:0.5, 1:0.75) were prepared by direct compression method. The active ingredient and other excipients were weighed according to the formulation (Table-1).
Silymarin and the polymers xanthan gum and guar gum with different concentrations, sodium lauryl sulphate (SLS), polyvinyl pyrrolidone (PVP K30) and lactose were mixed together in mortar and pestle separately to get uniform mixture. The blend was passed through sieve No.16. The blend was then lubricated with magnesium stearate uniformly and then compressed into tablets using tablet compression machine (Rimek, India).

**Table 1** Formulation of silymarin tablet.

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>Formulation Code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1:1:0.25 F2:1:0.5 F3:1:0.75 F4:1:0.25 F5:1:0.5 F6:1:0.75 F7 Without Polymer</td>
</tr>
<tr>
<td>Silymarin</td>
<td>140 140 140 140 140 140 140</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>35 70 105 - - - -</td>
</tr>
<tr>
<td>Guar gum</td>
<td>- - - 35 70 105 -</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>181 146 111 181 146 111 216</td>
</tr>
<tr>
<td>Poly vinyl pyrrolidone (PVP K30)</td>
<td>16 16 16 16 16 16 16</td>
</tr>
<tr>
<td>Sodium lauryl sulphate (SLS)</td>
<td>16 16 16 16 16 16 16</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>12 12 12 12 12 12 12</td>
</tr>
</tbody>
</table>

*Weight of each tablet = 400mg

**Table 2** Evaluation of silymarin blend.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk density* (gm/cc)</td>
<td>0.35 ± 0.04</td>
<td>0.34 ± 0.02</td>
<td>0.36 ± 0.03</td>
<td>0.33 ± 0.05</td>
<td>0.33 ± 0.07</td>
<td>0.33 ± 0.04</td>
<td>0.33 ± 0.07</td>
</tr>
<tr>
<td>Tapped density* (gm/cc)</td>
<td>0.41 ± 0.09</td>
<td>0.40 ± 0.02</td>
<td>0.41 ± 0.10</td>
<td>0.38 ± 0.05</td>
<td>0.38 ± 0.07</td>
<td>0.38 ± 0.05</td>
<td>0.38 ± 0.02</td>
</tr>
<tr>
<td>Angle of repose* (θ)</td>
<td>32°91' ± 0.53</td>
<td>33°84' ± 0.62</td>
<td>34°33' ± 0.51</td>
<td>33°37' ± 0.42</td>
<td>33°76' ± 0.75</td>
<td>32°79' ± 0.23</td>
<td>32°30' ± 0.37</td>
</tr>
<tr>
<td>Compressibility index* (%)</td>
<td>14.12 ± 0.24</td>
<td>14.28 ± 0.32</td>
<td>12.94 ± 0.41</td>
<td>13.28 ± 0.21</td>
<td>13.19 ± 0.53</td>
<td>12.40 ± 0.17</td>
<td>11.90 ± 0.19</td>
</tr>
<tr>
<td>Hausner ratio*</td>
<td>1.16 ± 0.11</td>
<td>1.16 ± 0.27</td>
<td>1.14 ± 0.41</td>
<td>1.15 ± 0.33</td>
<td>1.15 ± 0.21</td>
<td>1.14 ± 0.30</td>
<td>1.16 ± 0.12</td>
</tr>
</tbody>
</table>

*All values are expressed as mean ± SD (n=3)

**Evaluation of Blend**

The blend was evaluated for angle of repose, bulk density, tapped density, compressibility index and hausner ratio (Mutalik Srinivas et al., 2000; Pharmacopoeia of India, 1996) (Table-2).

**Evaluation of Tablets**

The formulated tablets were evaluated for hardness (Shah et al., 1997), friability, thickness and weight variation (Subrahmanyam, 1998). Twenty tablets were selected at random and weighed individually. The individual weighed were compared with average weight for determination of weight variation. For estimation of drug content (Subrahmanyam and Thimmasetty, 2002). Ten tablets were powdered and powder equivalent to 100mg of silymarin was dissolved in sufficient quantity of methanol and make up to 100 ml with methanol. From this 10ml was pipetted out into a 100 ml standard flask and make up to mark with phosphate buffer pH 7.4. The solution diluted suitably with phosphate buffer pH 7.4 and analyzed for drug content by UV-double beam spectrophotometer at 286 nm.

**IR Studies**

It was used to study the interactions between the drug and polymer. The drug and polymer must be compatible to produce a stable product. Drug and polymer interactions were studied by using FTIR (Shimadzu, Japan, Model-84005) (Sharma, 2005). IR Spectral Analysis of pure silymarin, Silymarin with highest proportion of polymers
Xanthan gum, Guar gum (1:0.75) were carried out. The peaks and patterns produced by the pure drug were compared with the combination of polymer (Rao et al., 2004).

**In-vitro Release Studies**

The *in-vitro* drug release studies of silymarin CR tablets were conducted for a period of 10-hours using USP type II apparatus (Rolex, India) at 37 ± 0.5°C at 50 rpm speed. The dissolution studies were carried out in 900ml of phosphate buffer pH 7.4. One tablet was used in each test. At every half an hour interval samples of 10ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume. After suitable dilution, the sample solution was analyzed by UV-double beam spectrophotometer. The amounts of drug present in the sample were evaluated with the help of appropriate calibration curve constructed from reference standard. The study was conducted in triplicate (Yeole et al., 2006).

**Stability Studies**

The stability was carried out on the optimized formulation. The stability studies were performed at 45º ± 2ºC and (75% ± 5% RH) for 45 days. At 15 days intervals the tablets were evaluated for the estimation of drug content and invitro drug release.

**Results and Discussion**

**Evaluation of Blend and Tablets**

The granules prepared for compression of tablets were evaluated for their properties. The angle of repose was within the range of 32º 30’ to 34º33’, bulk density was in the range of 0.33 to 0.36 g/cc, tapped density ranged from 0.38 to 0.41 g/cc, compressibility index was found to be 11.28 to 14.28% and Hausner ratio ranged from 1.12 to 1.16. All the parameters were within the limits, the result of blend was presented in Table 3.

After preparing the CR tablets, all the tablets formulations were subjected to various evaluation tests such as hardness, thickness, friability, uniformity of weight and estimation of drug content. The hardness of the tablets was found to be 4.78 to 5.56 kg/cm². The thickness of the tablets ranged form 4.02 to 4.30 mm. The friability of all the formulated tablets was found to be in the range of 0.20 to 0.70%. From the weight variation test, the average percentage deviation of 20 tablets ranged from 95.68 to 104.3%. Thus all the physical parameters of the various formulations were practically within the limits.

**IR Spectral Analysis**

The IR studies of pure Silymarin and formulations containing highest proportion of the polymers (1:0.75) were carried out to study the interaction between the drug and polymers used.

OH stretching, CH aliphatic stretching, C=O stretching, C=C stretching, Methylenic CH₂ stretching, O-H bending and aromatic vibration bending of pure silymarin and the silymarin controlled release tablets formulations containing higher proportion of the polymers were almost in the same region of wave number ranging from 3452.34cm⁻¹ to 649.97 cm⁻¹. The results proved that there were no significant interactions between the drug and polymers.

**In-vitro Release Studies**

From the *in-vitro* drug release studies, The percentage drug release of all formulations after 10 hours using xanthan gum was found to be 86.78% (silymarin: xanthan gum 1:0.25), 81.64% (1:0.5), 73.92% (1:0.75) and using guar gum was 88.27% (silymarin : guar gum 1:0.25), 84.85% (1:0.5), 79.09% (1:0.75). The results of the invitro release studies of all formulations are graphically represented as shown in Fig. 1.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardness* (kg/cm²)</td>
<td>5.16 ± 0.15</td>
<td>5.16 ± 0.67</td>
<td>4.92 ± 0.33</td>
<td>5.12 ± 0.47</td>
<td>4.8 ± 0.27</td>
<td>4.76 ± 0.38</td>
<td>4.78 ± 0.29</td>
</tr>
<tr>
<td>Friability* (%)</td>
<td>0.50 ± 0.03</td>
<td>0.40 ± 0.14</td>
<td>0.20 ± 0.05</td>
<td>0.70 ± 0.32</td>
<td>0.68 ± 0.05</td>
<td>0.45 ± 0.26</td>
<td>0.57 ± 0.08</td>
</tr>
<tr>
<td>Uniformity of weigh* (mg)</td>
<td>399.1 ± 2.3</td>
<td>400 ± 3.1</td>
<td>399 ± 2.8</td>
<td>398 ± 3.7</td>
<td>397 ± 4.1</td>
<td>399.4 ± 3.0</td>
<td>399 ± 2.5</td>
</tr>
<tr>
<td>Drug content* (%)</td>
<td>101.9 ± 0.60</td>
<td>98.03 ± 0.90</td>
<td>95.68 ± 0.22</td>
<td>103.92 ± 0.14</td>
<td>104.3 ± 0.26</td>
<td>100.7 ± 0.5</td>
<td>97.92 ± 0.30</td>
</tr>
<tr>
<td>Thickness* (mm)</td>
<td>4.1 ± 0.02</td>
<td>4.3 ± 0.01</td>
<td>4.1 ± 0.04</td>
<td>4.02 ± 0.06</td>
<td>4.3 ± 0.03</td>
<td>4.1 ± 0.07</td>
<td>4.2 ± 0.04</td>
</tr>
</tbody>
</table>

* All values are expressed as mean ± SD (n=3)
In-vitro release of silymarin from the formulation without polymer was found to be 99.0% in 3.5 hour.

When the polymer ratio was increased, the percentage drug release of silymarin was decreased from controlled release dosage form.

**Stability Studies**

The Stability Studies was performed on all formulations stored at 45°± 2°C (75 ± 5% RH). Tablet evaluation test includes drug content and in vitro release studies. There were no significant changes in the formulations.

**Conclusion**

Controlled release tablets of silymarin were prepared with two different polymers and evaluation of blend, tablet evaluation studies, IR spectral studies, dissolution studies and stability studies were performed. The results were presented.

From the above study, it was concluded that Silymarin may be formulated as controlled drug delivery system and all formulations showed that the drug release was at controlled manner.

In light of the aforementioned discussion, it could be concluded that both xanthan gum and guar gum can be used as an effective controlled release polymers to retard the release of silymarin for extended period of time. This study concluded that the inherent draw backs of conventional silymarin dosage form can be overcome by formulating it in controlled release tablets.

**References**


