Development and evaluation of pectin based colon targeted herbal drug delivery system

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Accepted 24 June, 2012

The objective of present investigation was to develop rhubarb matrix tablets intended for colon specific delivery system (CoSDS) using two combined approaches of biodegradable microflora-activated system with a pH-sensitive system. Matrix tablets of rhubarb were prepared by wet granulation method using polysaccharide, that is, pectin (10%) alone and in combination with hydrocolloids, that is, hydroxypropyl methylcellulose (HPMC) and hydroxyethylcellulose (HEC) in different concentration of 5, 10, and 15%. Each formulation was characterized in terms of hardness, friability, drug content, disintegration time and in vitro drug release study. On the basis of release profile in the presence of pectinase enzyme after 6 h, formulation containing 10% pectin with 10% HEC was selected as an optimized formulation which was not able to retard the drug release in stomach and upper intestine environment completely. So, it was further coated with eudragit S-100 (ES 100) as a pH sensitive polymer in different coat weight of 3 and 6% w/w. The results obtained reveal that pectin based matrix formulation containing 10% HEC with 6% coat weight of ES 100 exhibited a promising colon targeting performance. There was no significant variation found during stability studies.

Key words: Rhubarb, colon, pectin, hydrocolloids, eudragit S-100.

INTRODUCTION

Recently, greater emphasis has been placed on controlling site of drug release from oral formulations for the purposes of improving patient compliance and treatment efficiency. Colon specific drug delivery system is becoming increasingly popular for the treatment of colonic diseases. Constipation is a very complicated problem and to treat this complication many novel herbal alternative has been reported (Farzaneh et al., 2012). Safe and effective drugs from herbal origin are available as compared to few options available via allopathic drugs (Munira et al., 2007). Herbal extracts have always drawn much consideration, because of their multidimensional actions (Saraf et al., 2011).

*Rheum emodi* commonly known as revand-chini, family Polygonaceae, is a well-known herbal laxative drug and it was included in Ayurvedic and Unani systems of medicine (Indian Herbal Pharmacopoeia, 2002). The laxative action of rhubarb is obtained by stimulating colonic motility and accelerating colonic transit which reduces fluid absorption from the fecal mass and also by increasing paracellular permeability across the colonic mucosa, probably owing to an inhibition of Na+/K+ exchanging ATPase or to an inhibition of chloride channels. This results in an increase in the water content in the large intestine (Amin et al., 2009; Reynolds et al., 1993). This suggests its action in lower intestine, not in stomach and upper intestine. By targeting the entire quantity of drug in colon, we can minimize the possible loss of drug during passage through upper gastrointestinal tract.

The main approaches proposed to achieve colon-selective drug delivery include pH-sensitive systems, time-dependent systems, pressure controlled systems, prodrug and microflora activated systems (Chourasia...
Table 1. Composition of pectin based rhubarb matrix tablets.

<table>
<thead>
<tr>
<th>Ingredient (mg)</th>
<th>Formulation code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B1</td>
</tr>
<tr>
<td>Rhubarb extract</td>
<td>385</td>
</tr>
<tr>
<td>Pectin</td>
<td>60</td>
</tr>
<tr>
<td>HPMC</td>
<td>---</td>
</tr>
<tr>
<td>HEC</td>
<td>---</td>
</tr>
<tr>
<td>PVP-K30</td>
<td>42</td>
</tr>
<tr>
<td>Sodium lauryl sulphate</td>
<td>3</td>
</tr>
<tr>
<td>Dicalcium phosphate</td>
<td>92</td>
</tr>
<tr>
<td>Talc</td>
<td>12</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>600</td>
</tr>
</tbody>
</table>

B1 = Plain pectin matrix tablet; B2, B3, and B4 = 5, 10, and 15% HPMC- Pectin matrix tablet, respectively; B5, B6, and B7 = 5, 10, and 15% HEC- Pectin matrix tablet, respectively.

et al., 2003; Gliko-Kabir et al., 2006). Bacterially, degraded polysaccharides, particularly pectin, have potential value for such systems, because once the dosage form enters into colon, it is acted upon by polysaccharidases, which degrades pectin and releases the drug into the vicinity of bioenvironment of colon (Sinha et al., 2001; Ashford et al., 1993; Shirwaikar et al., 2008).

The main aim of the present study was the development of rhubarb matrix tablets intended for specific delivery of drug to the colon, by using pectin as a matrix carrier alone and in combination.

MATERIALS AND METHODS

Rhubarb roots were supplied by Sanjivani Aushdhalay, Bhavnagar, India. Roots were powdered and passed through 60 mesh screen. Emodin was purchased from Xian Scidoor Organic Tech Co Ltd., China. Eudragit S-100 was gifted by Evonik Degussa India Pvt. Ltd., Mumbai, India. Hydroxy propyl methyl cellulose (HPMC) and hydroxy ethyl cellulose (HEC) were gifted by Unique Pharmaceuticals Ltd., Ankleshwar, Gujarat. Polyvinylpyrrolidone K 30, dicalcium phosphate, sodium lauryl sulphate, magnesium stearate, and talc were provided by S.D. Fine Chemicals Ltd., Mumbai, India. Pectinase Enzyme was provided by Zydus Cadila Pharmaceuticals, Ahmedabad.

Method for extraction of rhubarb root

Methanolic extract was prepared by continuous extraction technique using Soxhlet’s apparatus. Dried powder of rhubarb root was extracted with methanol at 40°C, and lastly, the remaining concentrated extract was collected and dried at room temperature for 48 h (Akhtar et al., 2009).

Preparation of pectin based rhubarb matrix tablets

Pectin based matrix tablets of rhubarb were prepared by wet granulation process. First, dried rhubarb extract powder was mixed with mentioned quantity of pectin and polymer, sodium lauryl sulfate (0.5%), polyvinylpyrrolidone K 30 (7%), and dicalcium phosphate. Sufficient quantity of isopropyl alcohol was added to granulate dry powder blend. Wet granules were sieved through 22 mesh screen and were dried for 3 h at 40°C in tray drier. Finally, the dried granules were tapped on a 44 mesh screen to remove fines. The oversize granules were sequentially lubricated with talc (2%) and magnesium stearate (1%). The tablets with average weight of 600 mg were compressed using rotary tablet press (Cadmach Machines Ltd, Ahmedabad, India) with 11 mm concave punches. The composition of rhubarb matrix tablets is given in Table 1. The formulated tablets were analyzed for their physical characteristics as per standard methods. The crushing strength and friability of matrix tablets was determined by monsanto hardness tester (MHT-20, Campbell electronics, Mumbai, India) and Roche friabilator (EF2, Electrolab, India), respectively.

Preparation of coating solution

The optimized formulation was coated with eudragit S-100 (ES 100) to ensure the device more pH dependent and trigger the drug release only at colonic pH. 4 g of ES 100 was dissolved slowly in 80 ml of isopropyl alcohol with continuous stirring for 30 min using magnetic stirrer. To reduce tackiness of the tablets, the plasticizer (Castor oil) was added in the solution based on the solid dry weight (20% w/w) of ES 100 present and was mixed for 1 h. Solution of color (Amaranth blue) in 20 ml isopropyl alcohol was gradually added and stirred for 15 min.

Film coating process

The coating of rhubarb tablets was done by conventional coating pan (Model CPS, M/s Karnavathi engineering, Ahmedabad) at 30 rpm. The coating procedure involved maintaining the bed temperature at 25 to 30°C. The desired volume of the coating solution was sprayed on pre-warmed tablet (batch size 30 tablets) bed in a pan coater and was dried with the help of inlet air having temperature 35 to 40°C. The coating procedure was repeated till the desired level of coating (3 and 6% coat weight over tablet as % w/w) was achieved. The final drying stage was done by stopping the spraying of coating solution and keeping the coated tablets at the same bed temperature for 30 min.
Table 2. Physical characteristics of rhubarb matrix tablets.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Drug content (%)</th>
<th>DT (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>5.50 ± 0.26</td>
<td>0.405 ± 0.01</td>
<td>98.99 ± 0.47</td>
<td>10.97 ± 1.17</td>
</tr>
<tr>
<td>B2</td>
<td>5.67 ± 0.25</td>
<td>0.388 ± 0.02</td>
<td>99.66 ± 0.71</td>
<td>11.67 ± 1.44</td>
</tr>
<tr>
<td>B3</td>
<td>5.60 ± 0.30</td>
<td>0.399 ± 0.04</td>
<td>99.18 ± 1.06</td>
<td>11.10 ± 0.78</td>
</tr>
<tr>
<td>B4</td>
<td>5.57 ± 0.25</td>
<td>0.397 ± 0.02</td>
<td>99.28 ± 0.71</td>
<td>11.03 ± 1.01</td>
</tr>
<tr>
<td>B5</td>
<td>5.30 ± 0.20</td>
<td>0.452 ± 0.02</td>
<td>99.33 ± 1.14</td>
<td>10.47 ± 0.66</td>
</tr>
<tr>
<td>B6</td>
<td>5.70 ± 0.10</td>
<td>0.371 ± 0.03</td>
<td>99.74 ± 0.53</td>
<td>11.67 ± 0.60</td>
</tr>
<tr>
<td>B7</td>
<td>5.57 ± 0.15</td>
<td>0.396 ± 0.03</td>
<td>99.13 ± 0.61</td>
<td>11.07 ± 1.33</td>
</tr>
</tbody>
</table>

*Average of 3 determinations ± SD.

Drug content uniformity test
The rhubarb tablets were tested for their drug content. Ten tablets were finely powdered; quantities of the powder equivalent to 770 mg of rhubarb extract were accurately weighed and transferred to a 100 ml of volumetric flask. Initially, about 50 ml of 0.1 N HCl was added into volumetric flask and mixed thoroughly. The volume was made up to 100 ml with 0.1 N HCl and was filtered. Dilute 10 ml of the resulting solution to 250 ml with 0.1 N HCl and measure the absorbance of the resulting solution at the maximum at 444 nm using ultraviolet-visible (UV/VIS) spectrophotometer (Shimadzu UV 2450, double beam spectrophotometer, Japan). Estimate the rhubarb extract content (quantified as 20 mg emodin equivalent) in the tablet formulations (Gebre-Mariam et al., 2005; Heard et al., 2006).

In vitro drug release study
The ability of rhubarb tablets to remain intact in the physiological environment of stomach and small intestine were assessed by mimicking mouth to colon transit. Drug release studies were carried out using a USP dissolution apparatus II (50 rpm, 37 ± 0.5°C) for 2 h in simulated gastric fluid (900 ml of 0.1 N HCl) as the average gastric emptying time is about 2 h. Then, the dissolution medium was replaced with simulated intestinal fluid (900 ml pH 7.4 phosphate buffer) and was tested for drug release for 4 h as the average small intestinal transit time. After 6 h, the dissolution medium was replaced by simulated gastric fluid (900 ml pH 6.8 phosphate buffer) containing 4% w/v of pectinase enzyme and was tested for drug release up to 12 h. At the end of the specific time interval, 5 ml of the sample was withdrawn, filtered through Whatman filter paper (45 µ), and was analyzed for rhubarb extract content (quantified as 20 mg emodin equivalent) (Gebre-Mariam et al., 2005; Heard et al., 2006) using ultraviolet-visible (UV/VIS) spectrophotometer (Shimadzu UV 2450, double beam spectrophotometer, Japan). A 5 ml volume of fresh dissolution medium was added to make the volume after each sample withdrawal (Mura et al., 2003; Alvarez et al., 2004).

Stability studies
Stability studies were conducted for the optimized formulation OB2 at 25°C/60% relative humidity (RH) and 40°C/75% RH for 3 months as per ICH guidelines. After 3 months, the tablets were evaluated for their general appearance, drug content and in vitro drug release study (Sidney et al., 2000).

RESULTS AND DISCUSSION

Physical characteristics of rhubarb matrix tablets
The crushing strength and disintegration time (DT) of the matrix tablets was found to be in the range of 5.30 ± 0.20 to 5.70 ± 0.10 kg/cm² and 10.47 ± 0.66 to 11.67 ± 1.44 min for all formulations (B1 to B7), respectively. All the formulations showed friability in the range of 0.371 ± 0.03 to 0.452 ± 0.02%. The matrix tablets were found to contain 98.99 ± 0.47 to 99.74 ± 0.53% of rhubarb extract in each formulation. All the evaluated parameters (Table 2) were complied with compendial specifications.

In vitro drug release studies of rhubarb matrix tablets
For the drug delivery system designed for colon targeting, it is desirable that the system remains intact in the physiological environment of stomach, upper intestine and release the drug in the colon. For the present study, it is desirable to design the formulation such that it releases drug in the colon without loss of drug in the upper gastrointestinal tract (GIT).

The in vitro drug release data for all formulations of rhubarb extract is as shown in Figure 1. Formulation B1 (Plain Pectin matrix tablet) showed complete release of the drug at the end of 5 h. The release of the drug was found between 42 to 72% at the end of 6 h from formulations B2 to B4 (Pectin with different concentration of HPMC), while 7 to 31% drug was released from formulation B5 to B7 (Pectin with different concentration of HEC) at the end of 6 h. Formulation B7 containing 15% HEC released the drug very slowly even after 6 h and only 75.84% drug was released at the end of 12 h, while formulation B6 containing 10% HEC released the drug very satisfactorily even after 6 h, and complete drug release (99.59%) was found at the end of 12 h. Comparative release profile of all the formulations clearly indicated that the drug release is directly proportional to the amount of pectin and inversely proportional to the
amount of HPMC and HEC. The release pattern of formulations containing HEC was found satisfactorily and near to expected value than the formulations containing HPMC.

**Optimization of rhubarb matrix tablets**

On the basis of release pattern, it is very clear that the formulation B6 appears to be the most promising batch. As per the main prerequisite for a colon specific delivery system (CoSDS), optimized formulation containing 10% pectin with 10% HEC was not able to retard the drug release in stomach and upper intestine environment completely. Further to make the device more pH dependent and trigger the drug release only in colon, coating layer with ES 100 was given to optimized formulation. ES 100 was selected as a coating polymer due to its acid insoluble nature. Finally, optimized formulation was coated with ES 100 and coating procedure was continued till 3 and 6% coat weight over tablet was achieved.

**In vitro drug release studies of film coated rhubarb matrix tablets**

The *in vitro* release profile of formulations OB1 (with 3% coat weight) and OB2 (with 6% coat weight) (Figure 2) clearly indicated that the complete retardation of the drug was achieved from pectin based matrix tablet with 6% coat weight. The release of the drug after 6 h (after reaching colon) was also found to be satisfactorily from formulation OB2 than formulation OB1. Finally, formulation OB2 only exhibited a promising colon targeting performance during *in vitro* studies. Hence, formulation OB2 was chosen for stability studies as per ICH guidelines to access their stability.

**Stability studies**

Stability studies were performed to find out the effect of various temperature and humidity conditions on the formulation. The results indicated insignificant changes in its general appearance and drug content throughout stability study period (Table 3). Comparative release profile of formulation OB2 before and after stability studies is as shown in Figure 3. The profiles appeared to be almost super-imposable, which suggested that the drug release profiles investigated were therefore similar.

**Conclusion**

The present work was an attempt to develop CoSDS of rhubarb by using the combined approaches of biodegradable microflora-activated system and a pH-sensitive system. The amount of pectin and HEC and the coating levels over tablet had a significant effect on drug release pattern of tablet. The pH-dependent coating with ES 100 (6% w/w coat weight) of the pectin-based matrix tablet was coated with ES 100 and coating procedure was continued till 3 and 6% coat weight over tablet was achieved.
Figure 2. Effect of film coating on drug release.

Table 3. Data of drug content for formulation OB2 during stability study.

<table>
<thead>
<tr>
<th>Time (month)</th>
<th>Drug content (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At 25°C/60% RH</td>
</tr>
<tr>
<td>0</td>
<td>99.74 ± 0.53</td>
</tr>
<tr>
<td>1</td>
<td>99.61 ± 1.04</td>
</tr>
<tr>
<td>2</td>
<td>99.55 ± 1.32</td>
</tr>
<tr>
<td>3</td>
<td>99.52 ± 0.72</td>
</tr>
</tbody>
</table>

*Average of 3 determinations ± S.D.

Figure 3. In vitro drug release profiles of optimized formulation before and after stability study. OB2*: In vitro drug release study of formulation OB2 at 25°C/60% RH. OB2**: In vitro drug release study of formulation OB2 at 40°C/75% RH.
tablets containing 10% HEC was successful in adequately retarding the drug release, assuring the intact passing of the tablets through the upper GI tract, while maintaining intact the degradation effect of the enzymes and therefore the site specificity of the dosage form.

ACKNOWLEDGEMENTS

The authors wish to thank Shadhvi Shri Shijapiji, Campus Director, Veerayatan Vidypath, Jakhnia and Dr. G. Vidyasagar, Principal, Veerayatan Institute of Pharmacy for providing research platform and their technical assistance and inspiration to carry out the research work.

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