Formulation and In vitro Evaluation of Floating Tablets of Deglycyrrhizinized licorice


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Abstract

The present work was an attempt to formulate floating tablets of Deglycyrrhizinized licorice (DGL), aqueous extract of licorice root, using various polymers like HPMC K15, carbopol 934P and chitosan. Tablets were prepared by direct compression technique with altering the polymers and evaluated for physical properties, drug content, floating capacity and in vitro drug release. Physical characters and drug content studies of formulations did not show any significant variations and were found to have good physical integrity along with standardized amount. Incorporation of carbopol had significant impact on the release and floating property of DGL. The floating time was found to be 12 h with all formulations except when HPMC was used alone. However it was observed that the use of carbopol alone had insufficient release and the type of the polymer influences drug release pattern. A significantly (P<0.005) higher rate and extent of drug release was observed with formulations which contain both hydrophilic and lipophilic polymers. However, no significant difference in the drug release was observed among HPMC and chitosan at higher concentrations. Calculated regression coefficients showed a higher $r^2$ value with Higuchi model and first order kinetics. This study concluded that carbopol along with HPMC or chitosan in the ratio of 67:33 can be used to formulate floating tablets of DGL.

Keywords: Deglycyrrhizinized licorice; floating tablets; In vitro; HPMC; Chitosan; Carbopol

Introduction

Gastrointestinal transit time is one of the several physiological limitations that must be controlled in development of per oral sustained release dosage forms. This determines the time period available for drug release from oral controlled or sustained release dosage forms with in the gastrointestinal tract (GIT). Development of gastro retentive delivery systems (GRDS) have prolonged the gastric residence time of many drugs (Baumgartner et al., 2000; Dave et al., 2004; Owicki and Lunio, 2005) and thereby improves bioavailability (Streibel et al., 2003; Shimpi et al., 2004). Various researchers have attempted different techniques to enhance the oral bioavailability, reduce the drug waste and improve solubility for drugs that are less soluble in high pH environment. However, floating drug delivery system is found to be highly popular among the researchers due to its higher buoyancy and lower density than that of the gastric fluids (Machida et al., 1989). This delivery system is attractive for drugs which have absorption

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Ulceration occurs when there is a disturbance of the normal equilibrium caused by either enhanced aggression or diminished mucosal resistance. Several factors are implicated in the pathogenesis of gastric ulcer. These include increased acid-pepsin secretion, impaired bicarbonate neutralization, impaired mucus secretion; precipitate lesions on the mucus layer (Kent Lloyd and Debas, 1994) and are also associated with infection of gastrointestinal mucosal tissue by \textit{Helicobacter pylori} (Tepperman and Jacobson, 1994).

Licorice is a shrub native to southern Europe and Asia. The root part is used as sweetening agent and for medicinal purposes. Deglycyrrhizinized licorice (DGL), aqueous extract of root has been proven effective in healing gastric ulcers, soothing the mucous membranes of the digestive tract and peptic ulcers (Mills and Damrau, 1965; Dehpour et al., 1995; Russel et al., 1984; Fukai et al., 2002). Gastro retentive dosage form is considered to be an ideal delivery system in treating local gastric diseases like \textit{Helicobacter pylori} infected peptic ulcer in stomach (Tewari et al., 1968; Mitscher et al., 1980; Beil et al., 1995). In the present study an attempt has been made to develop floating tablets of DGL using different polymers and evaluated \textit{in vitro}.

\textbf{Materials and Methods}

\textit{Materials}

DGL was obtained as a gratis sample from Natural Remedies (Bangalore India). HPMC K15, carbopol 934P, chitosan, sodium bicarbonate, magnesium stearate and talc were purchased commercially. All other chemicals used were of analytical grade.

\textit{Analytical method}

Amount of DGL in the samples was quantified by high performance liquid chromatography (HPLC) system (Shimadzu, LC-10ATVP, Japan) consisting of a Phenomenex C18 analytical column (4.6 X 250 mm, Luna, 5.0 \( \mu \)m). Column was maintained at ambient temperature and the compounds were eluted at a flow rate of 1.5 ml/min. Acetonitrile and 1mM potassium dihydrogen phosphate containing 0.5ml of orthophosphoric acid (20:80) was used as mobile phase. Injection volume was 20 \( \mu \)l and the column effluent was monitored at 254 nm.

\textit{Preparation of tablets}

DGL tablets were prepared by direct compression technique. Respective ingredients (drug, polymer, and additives) were passed through sieve no. 80 and blended with a Turbula mixer (Analytical Technology, Bangalore, India). All the batches were compressed on a 10-station tablet punching machine (Cadmach, Ahmedabad, India) with 13 mm flat round punches. Three batches were prepared for each formulation. Formulations composition of DGL tablets were given in Table 1.

\textit{Characterization of tablets}

Physical properties of compressed floating tablets such as weight variation, friability and hardness were determined using standard procedures (Keith M., 1991). Weight variation of tablets was performed by randomly selecting twenty tablets and weighing them individually and together in a single pan balance (Shimadzu, AX200, Japan). Friability was tested by Roche friabilator (Electro Lab, EF-2, Mumbai, India). Tablets were weighed and allowed for 100 revolutions in 4 min and were dedusted. The
percentage loss was calculated by reweighing the tablets. Hardness was tested by commonly used Monsanto type tablet hardness tester (IEC, Mumbai, India) by placing a tablet between the anvils and the crushing strength, which causes the tablet to break, was recorded.

Drug content studies

Amount of drug in tablets was determined by randomly choosing five tablets of each formulation which were powdered using mortar and pestle. Powder equivalent to average weight of tablet was accurately weighed and dissolved in distilled water by sonication to ensure complete solubility of the drug. The sample was filtered, suitably diluted and analyzed by HPLC.

Floating capacity

Floating capacity of a tablet was determined by using dissolution apparatus (Electro Lab, TDT-08L, Mumbai, India), containing 900 ml of 0.1 M HCl at 75 rpm. Time taken by tablet to reach top from bottom of the jar (floating lag time) and duration for which tablet constantly floats on the surface of the medium (floating duration) were measured.

In vitro drug release studies

Drug release profile was evaluated in vitro using a standard USP paddle dissolution test apparatus (Electro Lab, TDT-08L, Mumbai, India). Dissolution study was carried out in 900 ml of 0.1 M HCl (Dave et al., 2004) for a period of 12 h. Temperature was maintained at 37±0.5°C and a constant paddle rotation speed of 75 rpm. Samples (10 ml) were withdrawn at regular intervals and the volume of dissolution medium was maintained by replacing the same volume of fresh medium. The samples withdrawn were then filtered through a membrane filter (pore size 0.22 μm) and were analyzed by using HPLC.

Kinetics of drug release

The in vitro release data of the floating tablets were evaluated kinetically by zero order kinetics, first order kinetics, Hixson Crowell and Higuchi models and the ideal kinetic models were estimated for drug release.

Results and Discussion

Many polymers have been reported to be efficient in formulating floating drug delivery systems. However the selection of suitable polymers is the main criteria in developing a successful floating drug delivery. We hypothesize that the usage of single or combination of different characteristic polymers will enable to formulate an optimized GRDG for DGL. Joint usage of HPMC and carbopol has been attempted by various researchers to develop mucoadhesive and floating drug deliveries (Khanna et al., 1997). However in case of HPMC, low viscous grades are generally preferred for longer floating time (Li et al., 2003). Recently chitosan has received great attention as a matrix for the controlled release of active agents (El-Gibaly, 2002). It is a biocompatible and biodegradable polysaccharide soluble only in aqueous media of low pH and is non toxic. Present study evaluated the usage of above mentioned polymers in formulating a floating drug delivery for DGL. In all the formulations, total weight was kept constant (600 mg), while the amount of polymers was varied. To assess the effect of HPMC K15 and carbopol 934P on the floating time, tablets were prepared using these polymers separately. However amount of sodium bicarbonate was kept constant (50 mg), as incorporation of larger amount of effervescent agent may cause quicker depletion of the tablet matrices which decreases floating duration though the CO₂ generated by effervesence get entrapped in the gel layer and help the tablet to become buoyant in less time. All the
formulations were prepared by direct compression technique and the detailed composition of the formulations are given in Table 1.

**Table 1. Composition (in mg/tablet) of 200 mg DGL* floating tablets**

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>DGL</th>
<th>HPMC K15</th>
<th>Carbopol 934 P</th>
<th>Chitosan</th>
<th>Sodium bicarbonate</th>
<th>Magnesium stearate</th>
<th>Talc</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>200.00</td>
<td>338.00</td>
<td>-</td>
<td>-</td>
<td>50.00</td>
<td>6.00</td>
<td>6.00</td>
</tr>
<tr>
<td>L2</td>
<td>200.00</td>
<td>-</td>
<td>338.00</td>
<td>-</td>
<td>50.00</td>
<td>6.00</td>
<td>6.00</td>
</tr>
<tr>
<td>L3</td>
<td>200.00</td>
<td>169.00</td>
<td>169.00</td>
<td>-</td>
<td>50.00</td>
<td>6.00</td>
<td>6.00</td>
</tr>
<tr>
<td>L4</td>
<td>200.00</td>
<td>-</td>
<td>169.00</td>
<td>169.00</td>
<td>50.00</td>
<td>6.00</td>
<td>6.00</td>
</tr>
<tr>
<td>L5</td>
<td>200.00</td>
<td>225.40</td>
<td>112.60</td>
<td>-</td>
<td>50.00</td>
<td>6.00</td>
<td>6.00</td>
</tr>
<tr>
<td>L6</td>
<td>200.00</td>
<td>-</td>
<td>112.60</td>
<td>225.40</td>
<td>50.00</td>
<td>6.00</td>
<td>6.00</td>
</tr>
</tbody>
</table>

* Deglycyrrhizinated licorice

Physical properties of the formulations did not show any significant variations and were found to have good physical integrity (Table 2). Weight variation study was also found to be insignificant (P>0.001). Hardness of the prepared tablets was found to be 4 - 4.8 Kg/cm². Drug content study showed that amount between the formulations did not vary by more than 5% and were in the range of 96.83 to 103.51%.

**Table 2. Characteristics of DGL* floating tablets**

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Average Weight (mg)</th>
<th>Hardness (Kg/cm²)</th>
<th>Friability (%)</th>
<th>Drug content (%)</th>
<th>Floating Lag Time (sec)</th>
<th>Floating Duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>601.5 ± 2.25</td>
<td>4.0 ± 0.32</td>
<td>0.115 ± 0.01</td>
<td>96.83 ± 1.55</td>
<td>50 ± 1.27</td>
<td>4 ± 0.83</td>
</tr>
<tr>
<td>L2</td>
<td>600.8 ± 1.98</td>
<td>4.2 ± 0.29</td>
<td>0.104 ± 0.01</td>
<td>98.00 ± 1.96</td>
<td>0 ± 0.00</td>
<td>12 ± 1.30</td>
</tr>
<tr>
<td>L3</td>
<td>599.5 ± 2.23</td>
<td>4.6 ± 0.41</td>
<td>0.136 ± 0.01</td>
<td>102.12 ± 1.48</td>
<td>15 ± 0.81</td>
<td>12 ± 1.94</td>
</tr>
<tr>
<td>L4</td>
<td>602.2 ± 2.65</td>
<td>4.8 ± 0.35</td>
<td>0.122 ± 0.01</td>
<td>103.51 ± 1.99</td>
<td>20 ± 1.13</td>
<td>12 ± 1.81</td>
</tr>
<tr>
<td>L5</td>
<td>600.4 ± 1.59</td>
<td>4.4 ± 0.37</td>
<td>0.098 ± 0.00</td>
<td>98.22 ± 1.23</td>
<td>25 ± 1.57</td>
<td>12 ± 1.65</td>
</tr>
<tr>
<td>L6</td>
<td>599.8 ± 1.94</td>
<td>4.0 ± 0.33</td>
<td>0.112 ± 0.01</td>
<td>101.14 ± 1.84</td>
<td>18 ± 1.49</td>
<td>12 ± 1.08</td>
</tr>
</tbody>
</table>

*Deglycyrrhizinated licorice
Figure 1. *In vitro* release profiles showing the effect of polymers on DGL floating tablets. Each data represents the mean ± SE of six experiments, (●) HPMC K15, (■) Carbopol 934P, (▲) HPMC K15: Carbopol 934P (50:50), (×) Carbopol 934P: Chitosan (50:50), (+) HPMC K15: Carbopol 934P (67:33), (▲) Chitosan (67:33): Carbopol 934P.

Floating capacity of the prepared tablets was determined in 0.1 M HCl and the results were depicted in Table 2. It can be seen that formulation L1 (with HPMC) have showed only 4 h floating while all other formulations (L2 –L6) showed higher floating time and were not significantly different (P>0.001). The low floating time by batch L1 may be attributed to the low viscosity and fast hydration of HPMC. In contrast, formulation L2 (with carbopol) had an improved floating time, indicated its capacity to float for long time when used alone which is in agreement with an earlier report, where it has been described that the low density of the polymer helps in immediate floating (Alexander et al., 2006). Figure 1 shows the *in vitro* drug release profiles of different DGL formulations. It is evident from the figure that there was significant difference in drug release pattern from the formulation L1 (HPMC alone) and the drug release was completed in 4 h. As mentioned above the hydrophilic nature, fast hydration and low viscosity of the polymer maybe attributed to this. However in remaining formulations the apparent drug release rate observed were quite similar through out the study period and was steady due to polymer controlled release and appears to be single phase. The percentage of drug released from formulations L2, L3, L4, L5 and L6 after 10 h were found to be 48.65, 62.47, 71.62, 78.64 and 85.45% respectively.

Among the formulations, L2 had shown the minimum drug release, with an over all 54% in 12 h. These data indicate that the use of carbopol 934P alone appears to decrease the overall DGL release from the GRDS. Further it can be explained as the type of the polymer influences the release pattern of DGL. Carbopol is insoluble in water and simulated gastric fluid, under the test condition (0.1 M HCl). It has been reported that the swelling behavior of this polymer is attributed to the uncharged –COOH group that get hydrated by forming hydrogen bonds with the imbibing water and extending the polymer chain (Li et al., 2003). Formulations without carbopol (L1) exhibited a much higher burst effect, likely due to the fact that carbopol is a cross-linked polymer with high molecular weight, viscosity and when exposed to aqueous media, it would swell and hold water inside its microgel network. This particular property may partially be responsible for the retarded release of DGL from the GRDS. Data obtained have
confirmed that the release of DGL from carbopol polymer was steady throughout the study period.

Slight difference in DGL release pattern was observed when different combination of HPMC/chitosan was combined with carbopol. From figure 1, it appears that the incorporation of carbopol 934P with hydrophilic polymer (HPMC) (50:50) have significantly increased (P<0.05) drug release from initial hour itself. A similar result with higher drug release from 5 h was recorded when HPMC was replaced by chitosan (formulation L4), another hydrophilic polymer. Here too the drug release was not complete and the total release after 12 h was found to be only 80%. To further increase the release rate, in next stage, the ratio of hydrophilic to hydrophobic polymers was varied (67:33). The percentage of DGL released increased significantly (P<0.005) at the end of 12 h with 91 and 94% with batch L5 and L6 respectively. However there was no significant effect (P>0.001) in the drug release rate when carbopol was combined with HPMC or chitosan at 67:33 ratio due to similar behavior of these two formulations under the same condition, when analyzed statistically. It can also be said that there should be optimum balance between hydrophilic and lipophilic polymers to get the required release rate and floating time of the hydrophilic drug (DGL).

Table 3. Calculated kinetics value (r²) for the DGL* floating tablets.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Zero order Kinetics</th>
<th>Higuchi Model</th>
<th>First order Kinetics</th>
<th>Hixson Crowell Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>0.7746</td>
<td>0.9247</td>
<td>-0.9943</td>
<td>-0.9645</td>
</tr>
<tr>
<td>L2</td>
<td>0.9830</td>
<td>0.9960</td>
<td>-0.9950</td>
<td>-0.9927</td>
</tr>
<tr>
<td>L3</td>
<td>0.9838</td>
<td>0.9994</td>
<td>-0.9994</td>
<td>-0.9965</td>
</tr>
<tr>
<td>L4</td>
<td>0.9883</td>
<td>0.9996</td>
<td>-0.9977</td>
<td>-0.9991</td>
</tr>
<tr>
<td>L5</td>
<td>0.9858</td>
<td>0.9994</td>
<td>-0.9985</td>
<td>-0.9980</td>
</tr>
<tr>
<td>L6</td>
<td>0.9784</td>
<td>0.9940</td>
<td>-0.9969</td>
<td>-0.9928</td>
</tr>
</tbody>
</table>

* Deglycyrrhizinated licorice

The calculated regression coefficients showed a higher r² value with Higuchi model and first order kinetics (Table 3). It can also be seen that though there was no significant difference (P>0.01) observed between these two models, a higher r² value was recorded with Higuchi models. However the regression values were found to be low with zero order kinetics an Hixson Crowell models. Hence it can be said that the release of DGL, hydrophilic drug, from the formulations fit with the Higuchi model equation of diffusion from the matrix.

In nutshell it can be said that carbopol along with HPMC or chitosan in the ratio of 67:33 can be used for preparation of floating tablets of DGL. The observed difference in drug release an floating property may be attributed to the difference in the basic properties of three polymers due to their water uptake potential and functional group substitution.
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References


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