Design and development of guar gum and borax crosslinked guar gum matrix tablets of theophylline for colon specific drug

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ABSTRACT

The present study was carried out to develop an oral colon targeted drug delivery system, which consists of Theophylline matrix tablets prepared using guar gum and borax cross linked guar gum as rate controlling polymers in different concentrations. These tablets were evaluated for weight variation, friability, hardness uniformity of content and in vitro drug release under specified conditions. The dissolution data revealed that the tablets containing guar gum and borax cross linked guar gum in higher concentrations each (120mg) showed 87.567±0.42% and 76.186±0.17% of drug release respectively. And selected tablets of borax cross linked guar gum were subjected to in vitro drug release study in presence of rat caecal content medium. Results clearly indicate that there is an increase in the release of the drug to 98.930±0.38%.

Key words: Theophylline, Guar gum, Borax cross linked guar gum.

INTRODUCTION

Targetting of drugs to specific sites gaining more attention today as we can increase the efficacy, reduce the undesirable effects of drugs with the site specificity. Now a days Colon specific drug delivery is not only used for the delivery of peptides and proteins which are susceptible to degradation in the upper parts of the gastro intestinal tract but also for the delivery of drugs which are used to treat the diseases associated with the colon, large intestine such as ulcerative colitis, diarrhea and colon cancer. Colon drug delivery is usually employed to achieve one of the four objectives, the desired outcomes can be (a) sustained delivery to reduce dosing frequency; (b) to delay delivery to the colon to achieve high local concentrations in the treatment of diseases of the distal gut (c) to delay delivery to a time appropriate to treat acute phases of diseases (chronotherapy) (d) to deliver to a region that is less hostile metabolically e.g. to facilitate absorption of acid and enzymatically labile materials, especially peptides. Approaches used in the colon delivery of drugs include use of prodrugs, pH sensitive polymer coating, time dependent formulations, bacterial degradable coatings, and intestinal luminal pressure controlled colon delivery capsules.

Guar gum is a natural polysaccharide obtained from the endosperm of the Cyamopsis tetragonoloba belongs to the family Leguminosae.
EXPERIMENTAL SECTION

2.1 Materials
Theophylline and guar gum were obtained as a gift sample from Natco-Pharma Pvt. Ltd, Hyderabad, India. Ethanol and Disodium tetra borate (borax) were procured from S.D. Fine Chemicals Mumbai, India. All other reagents used in the study were of analytical grade.

2.2 Methods

2.2.1 Preparation of borax guar gum
4 gms of guar gum was dispersed for 1 hr at room temperature in 400 ml of distilled water with the help of mechanical stirrer. The dispersion was kept aside for 2 hrs for swelling. 80 ml of 1% w/v aqueous solution of borax (disodium tetra borate) was added to the guar gum dispersion and stirred for 30 min with the help of mechanical stirrer then kept aside for another 4 hrs without stirring. The formed hydrogel was rinsed with distilled water to remove untreated borax and then the hydrogel was dried at room temperature for 3 days. The dried Borax cross linked guar gum was triturated in a mortar for size reduction and passed through sieve no 100.

2.2.2 Estimation of free borax and cross linked borax by titration with 0.05N HCl:
200 mg of guar gum was taken in conical flasks and dispersed in 30 ml of distilled water to make uniform dispersion. To the dispersion, methyl red was added and titrated against 0.05M HCl solution. The guar gum dispersion titrate value was taken as blank value. 200 mg of borax cross linked guar gum was taken in conical flasks and dispersed in 30 ml of distilled water to make uniform dispersion. To the dispersion methyl red was added and titrated against 0.05 M HCl solution. Titrate value was taken as free borax value. In the same way again 200 mg of borax cross linked guar gum was taken and dispersed in 30 ml of distilled water to make uniform dispersion. The dispersion was heated at 70°C to break the cross linked bonds of borax with guar gum and then to the dispersion methyl red was added and titrated against 0.05 M HCl solution and the results are shown in Table 1.

It is direct titration of strong alkaline borax with strong acid HCl. One mole of borax reacts with 2 moles of HCl. Methyl red is used as an indicator because it is not affected by weak acid (Boric acid) end point is colour change from yellow to pink.

\[
\begin{align*}
\text{Na}_2\text{B}_4\text{O}_7 + 2\text{HCl} & \rightarrow 2\text{NaCl} + 4\text{H}_3\text{BO}_3 + 5\text{H}_2\text{O} \\
\text{B}_4\text{O}_{10}\text{H}_2\text{O} + 2\text{HCl} & \rightarrow 2\text{NaCl} + 4\text{H}_3\text{BO}_3 + 5\text{H}_2\text{O}
\end{align*}
\]

2.2.3 Preparation of Theophylline matrix tablets
Theophylline matrix Tablets were prepared by wet granulation technique using PVPK30 as binder in IPA. All the ingredients as mentioned in Table 2 were passed through sieve No. # 40 mesh except magnesium stearate and talc (#80 mesh), powder was thoroughly mixed and granulated until dough mass formed. Granules were prepared by passing through sieve no 16 and were lubricated with talc and magnesium stearate then compressed in to tablets on a 16-station rotary tablet punching machine (M/S. Cadmach Machinery Co. Pvt. Ltd., India) fitted with 9 mm round, standard concave punches with hardness at a range of 5-7 Kg/cm².

2.2.4 Rheological studies of Guar gum and Borax cross linked Guar gum
Viscosity of 1% w/v dispersion of Guar gum and Borax cross linked Guar gum in water, 0.1N HCl, pH 7.4 and pH 6.8 Phosphate Buffers was measured by using Brookfield viscometer and results are shown in Table 3.

2.2.5 Swelling studies of Guar gum and Borax cross linked Guar gum
Swelling capacity of both Guar gum and Borax cross linked Guar gum was studied in distilled water, 0.1N HCl, pH 7.4 and pH 6.8 phosphate buffers
1gm of gum was taken in a measuring cylinder to this 10 ml of distilled water was added and shaken vigorously for 10min and allowed to stand for 24hrs. Swelling capacity can be determined by,

\[
\text{Swelling Capacity} (\% v/v) = [X_r - X_i] \times 100
\]
Where $X_v$ denotes the final volume occupied by swollen material after 24 hrs and $X_i$ denotes the initial volume of the powder in graduated measuring cylinder.

Same procedure was repeated to study the swelling capacity of both gums in 0.1N HCl, pH 6.8 and pH 7.4 phosphate buffers and results are shown in table 4.

2.2.6 Evaluation of tablets
Formulated tablets were evaluated for the following physicochemical characteristics like weight variation, hardness, friability, uniformity of drug content and all the tablets followed the official compendial standards as per the I.P. specifications, results are shown in table 5.

2.2.7 In vitro dissolution studies:
Dissolution studies were carried out using USPXXII, type I apparatus (Model: DISSO 2000, M/s. Lab India) at 100 rpm. The tablets were placed in 900 ml of simulated gastric fluid (pH 1.2) for 2 hr, simulated intestinal fluid (pH 7.4) for 3 hr and simulated colonic fluid (pH 6.8) for 19 hr. sampling was done at regular time intervals and the same were estimated for drug content after suitable dilution by using double beam UV-visible spectrophotometer and drug release profiles are shown in fig1.

2.2.7.1 Preparation of rat caecal medium:
In vitro drug release studies were performed in the presence of rat caecal content after 5 hrs of dissolution (first 2 hrs in 0.1 N HCl and another 3 hrs in pH 7.4 Phosphate buffer). The albino rats weighing between 150-200 gm were selected and 1 ml of 1% w/v solution of borax cross linked guar gum was administered with the help of teflon tubing directly into the esophagus region via oral cavity. The treatment was continued for 6 days to induce enzyme responsible Borax guar gum degradation, animals were sacrificed before 30 min of dissolution studies and the caecum was exteriorized for content collection. The caecal content (anaerobic) was immediately transferred into buffer saline solution of pH 6.8 and 2%w/v concentration of solution was prepared by diluting with pH 6.8 phosphate buffer which was bubbled with CO$_2$ to maintain the anaerobic environment. Dissolution studies were carried out using USPXXII type I (basket) dissolution test apparatus. As the caecum is anaerobic in nature, the experiment was carried out with continuous CO$_2$ supply into the dissolution apparatus.5 ml of the samples were withdrawn at regular time intervals for about 19 hrs and the volume was replaced with fresh medium.

2.2.8 Drug release kinetics
Drug release from the tablets can be explained by two different methods, Model dependent and model independent methods.

In model-dependent approach, the dissolution data can be fitted to five popular release models such as zero-order, first-order, higuchi diffusion, hixson-crowell erosion and Korsmeyer-Peppas equations.

### Mathematical models for comparison of the dissolution profiles

<table>
<thead>
<tr>
<th>Model</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero-order</td>
<td>$Q_t = Q_0 + k_0 t$</td>
</tr>
<tr>
<td>First-order</td>
<td>$\ln Q_t = \ln Q_0 - k_1 t$</td>
</tr>
<tr>
<td>Higuchi</td>
<td>$Q_t = k_H \sqrt{t}$</td>
</tr>
<tr>
<td>Hixon-Crowell</td>
<td>$Q_o^{1/3} - Q_t^{1/3} = k_s t$</td>
</tr>
<tr>
<td>Korsmeyer-Peppas</td>
<td>$Q_t / Q_\infty = k_k t^n$</td>
</tr>
</tbody>
</table>

$Q_i$: amount of drug released in time $t$, $Q_0$: initial amount of drug in the Tablet, $Q/Q_\infty$: fraction of drug released at time $t$, $k_0$, $k_1$, $k_H$, $k_s$, $k_k$: release rate constants, $n$: the release exponent indicative of the mechanism of drug release. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from matrix systems was studied by using higuchi or erosion equation. The $n$ value is obtained as a slope for different batches of matrix tablets by plotting log percent drug dissolved against log time. If the value of $n = 0.45$ indicates Fickian (case I) release; $0.45 < n < 0.89$ for non-Fickian (anomalous) release.
n=0.89 case II and > 0.89 indicates super case II transport. Case II generally refers to the erosion of the polymeric chain and non-Fickian diffusion refers to a combination of both diffusion and erosion mechanism from the controlled drug release tablets\textsuperscript{11}.

**Infrared Spectroscopy Studies:**
The IR spectra of pure drug and the optimized formulation (pure drug with Borax cross linked guar gum) were recorded using KBr pellet technique (1:100) at resolution rate of 4cm\(^{-1}\). Spectrum was integrated in transmittance mode at the wave number range 400-4000cm\(^{-1}\).

**RESULTS AND DISCUSSION**

**3 Tableting parameters**
All the prepared tablets comply with the compendial standards for uniformity of weight and drug content uniformity as per the I.P. specifications. Hardness and friability values were found to be in the range of 5-7 kg/cm\(^2\) and the results are shown in Table 5.

**3.1 Drug release profiles**
Drug release profiles of guar gum and borax cross linked guar gum are presented in fig 1,2and 3 from the results it was observed that the as the concentration of guar gum increased from 60 to 140 mg there was decrease in drug release rate which was due to high viscosity of guar gum. When the guar gum was replaced by borax cross linked guar gum of same concentration drug release was further controlled which was due to the increase in viscosity and less swelling Index of the borax cross linked guar gum compared with guar gum. Increase in viscosity allows the drug to travel along the longer diffusional path. When the dissolution of the formulation F10 was carried in presence of caecal content maximum amount of drug was released compared to dissolution of formulation F10 in medium without out caecal content indicating the enzyme dependent degradation of borax guar gum.

**3.2 kinetic analysis of the dissolution data**
All the prepared formulations were fit in to popular models like zero order, first order,higuchi,erosion and peppas equations and the results are shown in table 6 results of drug release kinetics showed that all the formulations followed zero order release from the higuchi and equations it was found that F1,F2,F3formulations followed non fickian diffusion mechanism while the remaining followed erosion mechanism.

**3.3 IR spectra analysis**
From the IR spectra it was concluded that the drug was compatible with the all excipients used in the formulation.

**Table no 1:- Titration of 200 mg of Guar Gum, Borax Cross linked Guar Gum and Borax Cross linked Guar Gum While Heating**

<table>
<thead>
<tr>
<th>S. No</th>
<th>Contents in Conical Flask</th>
<th>Burette reading</th>
<th>Titer Value ml</th>
<th>Amount of Borax Present in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>200 mg of Guar Gum + 30 ml Water</td>
<td>50</td>
<td>49.8</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>200 mg of Borax Cross linked Guar Gum + 30 ml Water</td>
<td>49.8</td>
<td>49.4</td>
<td>0.4</td>
</tr>
<tr>
<td>3</td>
<td>200 mg of Borax Cross linked Guar Gum + 30 ml Water While heating</td>
<td>49.4</td>
<td>46</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Unreacted B\(_4\)O\(_7\)^- present in 200 mg of Borax crosslinked Guar Gum is 0.766 mg  
Unreacted B\(_4\)O\(_7\)^- present in 1g of Borax crosslinked Guar Gum is 3.83 mg  
Crosslinked B\(_4\)O\(_7\)^- present in 200 mg of Borax crosslinked Guar Gum is 11.5

**Table 2: Formulation of Theophylline tablets with guar gum and borax cross linked guar gum**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>F10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theophylline</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Guar Gum</td>
<td>60</td>
<td>80</td>
<td>100</td>
<td>120</td>
<td>140</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borax Guar Gum</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>60</td>
<td>80</td>
<td>100</td>
<td>120</td>
<td>140</td>
</tr>
<tr>
<td>PVP K 30 (3%)</td>
<td>8</td>
<td>8.5</td>
<td>9</td>
<td>9.5</td>
<td>10</td>
<td>8</td>
<td>8.5</td>
<td>9</td>
<td>9.5</td>
<td>10</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Talc</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Total weight</td>
<td>274</td>
<td>294.5</td>
<td>315</td>
<td>335.5</td>
<td>356</td>
<td>356</td>
<td>356</td>
<td>356</td>
<td>356</td>
<td>356</td>
</tr>
</tbody>
</table>
Table 3: Viscosity studies of 1% w/v Dispersions of Guar gum and Borax cross linked guar gum

<table>
<thead>
<tr>
<th>1% w/v Dispersion of Polymer</th>
<th>Viscosity in Water(cps)</th>
<th>Viscosity in 0.1 N HCl(cps)</th>
<th>Viscosity in pH 6.8 Phosphate Buffer(cps)</th>
<th>Viscosity in pH 7.4 Phosphate Buffer(cps)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guar gum</td>
<td>114.7</td>
<td>110.3</td>
<td>113.1</td>
<td>117.4</td>
</tr>
<tr>
<td>Borax guar gum</td>
<td>181.2</td>
<td>177.9</td>
<td>179.7</td>
<td>184.6</td>
</tr>
</tbody>
</table>

Table 4: Swelling index studies of guar gum and borax treated guar gum

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Swelling Index in Water</th>
<th>Swelling Index in 0.1 N HCl</th>
<th>Swelling Index in pH 6.8Phosphate Buffer</th>
<th>Swelling Index in pH 7.4Phosphate Buffer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guar gum</td>
<td>8.5</td>
<td>9.1</td>
<td>8.7</td>
<td>8.4</td>
</tr>
<tr>
<td>Borax guar gum</td>
<td>5.1</td>
<td>5.6</td>
<td>5.3</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Table 5: Physical properties of the Theophylline tablets formulated with various polymers.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Theoretical weight</th>
<th>Average weight</th>
<th>% Drug content</th>
<th>Hardness kg/cm²</th>
<th>% Friability</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>F2</td>
<td>101</td>
<td>101</td>
<td>101</td>
<td>101</td>
<td>101</td>
</tr>
<tr>
<td>F3</td>
<td>102</td>
<td>102</td>
<td>102</td>
<td>102</td>
<td>102</td>
</tr>
<tr>
<td>F4</td>
<td>103</td>
<td>103</td>
<td>103</td>
<td>103</td>
<td>103</td>
</tr>
<tr>
<td>F5</td>
<td>104</td>
<td>104</td>
<td>104</td>
<td>104</td>
<td>104</td>
</tr>
</tbody>
</table>

Fig 1: Comparative Dissolution Profiles of Theophylline matrix Tablets Formulated with Guar gum (F1 to F5):
Fig 2: Comparative Dissolution Profiles of Theophylline Tablets Formulated with Borax cross linked guar gum (F6 to F10)

Fig 3: Comparative Dissolution Profiles of Theophylline Formulations F5 (best formulation with Guar gum) and F10 (best formulation with Borax Cross linked Guar gum) Without Caecal Content and With Caecal Content
Fig 4: IR Spectrum of formulation

Fig 5: IR Spectrum of formulation
Guar gum a naturally occurring polymer can be used for the colon targeting of the drugs in the present research guar gum was crosslinked with the borax to enhance the viscosity of the gum there by increasing its efficiency as controlled release polymer. Amount of free borate in the formulation was estimated by titrimetry. Viscosity and swelling studies were conducted for guar gum as well as crosslinked guar gum form the results it was observed that crosslinking with borax enhanced the viscosity and reduced the swelling of the polymer. Formulations were prepared as per Table 1 by wet granulation technique and the granules were compressed using 16 station rotary compression. Prepared tablets were evaluated for quality control parameters and results are shown in Table 5.Dissolution studies were performed for all the formulations in 0.1N HCl (pH 1.2) for first two hours, simulated intestinal fluid (pH 7.4) for 3 hr and simulated colonic fluid (pH 6.8) for 19 hr. Comparative dissolution profiles of Theophylline matrix tablets formulated with guar gum are shown in figures 1-3. Dissolution data was fitted in to popular kinetic models like Higuchi, Hixon-Crowell cube root model,Peppas and values are given in table 6 from the kinetic analysis of the data it was shown that optimized formulation F10 followed zero order release with non-fickian diffusion mechanism in the absence of caecal content and it followed erosion mechanism in the presence of caecal content indicating the degradation of polymer in the presence of colonic microflora . The IR spectra of the pure drug and best formulation indicated that no chemical interaction occurred between the drug, Theophylline and the carriers used.

CONCLUSION

In this study the influence of cross linking agent borax on drug release characteristics was studied. The cross linking of borax on guar gum can increase the viscosity and reduce the swelling index of the polymer so the cross linking can retard the drug release efficiently when compared to normal guar gum. Cross linked guar gum was estimated for the determination of any free borate ions by titrimetry. Dissolution profiles of formulations formulated with the guar gum and borax cross linked guar gum were compared and results showed that cross linked guar gum controlled the drug release efficiently than the untreated guar gum; this was further conformed by the swelling studies of the formulations. Maximum amount of the drug was released in the presence of caecal content it can be correlated with the drug release in the colon due to microbial degradation. From this study it was concluded that borax cross linked guar gum a novel polymer can be used as controlled release polymer.

REFERENCES