Matrix tablet containing various proportion of guar gum were prepared by wet granulation technique using starch as a binder. All the formulation were evaluated for hardness, drug content uniformity, stability study, and were subjected to in-vitro drug release studies. The amount of tinidazole released from the matrix tablet at different time interval was estimated by UV method. Colon targeted matrix tablet of tinidazole containing 40% guar gum released 7% of tinidazole in the physiological environment of stomach (0.1N HCl) & small intestine (phosphate buffer 7.4 pH) & 91% in the physiological environment of colon (phosphate buffer 6.8 pH). When the dissolution study was continued in simulated colonic fluids (rat caecal content medium) the matrix tablet containing 40% guar gum released another 98% of tinidazole after degradation into 2-3 pieces at the end of 24 h study. The result of the studies showed that colon targeted matrix tablet containing 40% of guar gum was most likely to provide targeting of tinidazole for local action in the colon. The colon targeted matrix tablet of tinidazole showed no change either in physical appearance, drug content or in dissolution pattern after storage at 40°C/75% RH for 2 months. IR spectrum showed no interaction between tinidazole & guar gum.

**Keywords:** Colon targeted matrix tablet, Tinidazole, Guar gum, Rat caecal content

**INTRODUCTION**

The oral route is considered to be most convenient for administration of drugs to patients. Oral administration of conventional dosage forms normally dissolves in the stomach fluid or intestinal fluid and absorb from these regions of the gastrointestinal tract (GIT) depends upon the physicochemical properties of the drug. It is a serious drawback in conditions where localized delivery of the drugs in the colon is required or in conditions where a drug needs to be protected from the hostile environment of upper GIT. Dosage forms that deliver drugs into the colon rather than upper GIT proffers number of advantages. Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon (ulcerative colitis, Crohn’s disease, carcinomas and infections) whereby high local concentration can be achieved while minimizing side effects that occur because of release of drugs in the upper GIT or unnecessary systemic absorption. The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery. The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability. This region of the colon is recognized as having a somewhat less hostile environment with less diversity and intensity of activity than the stomach and small intestine. Additionally, the colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs. Apart from retarding or targeting dosage forms, a reliable colonic drug delivery could also be an important starting position for the colonic absorption of perorally applied, undigested, unchanged and fully active peptide drugs. As the large intestine is relatively free of peptidases such special delivery systems will have a fair chance to get their drug sufficiently absorbed after peroral application. The simplest method for targeting of drugs to the colon is to obtain slower release rates or longer release periods by the application of thicker layers of conventional enteric coatings or extremely slow releasing matrices.

**METHODOLOGY**

**Formulation Of Colon Targeted Matrix Tablet Of Tinidazole**

Matrix tablet of tinidazole were prepared by the wet granulation technique using 10% starch paste. Microcrystalline cellulose was used as diluent and the mixture of talc & magnesium stearate at 2:1 ratio was used as lubricant. The composition of different matrix formulation used in the study containing 150 mg of tinidazole given in table 6. In the all formulation guar gum was sieved (250 µm or sieve no. 60) separately and mixed with tinidazole (150µm or sieve no. 100) and microcrystalline cellulose (250 µm or sieve no. 60). The powder were blended and granulated with 10% starch paste. The wet mass was obtained which as then passed through a mess (1190 µm). And the wet granules were dried at 50°C for 2 hours. The dried granules were passed through a mess (1000 µm or sieve no.16) and were lubricated with a mixture of talc & magnesium stearate (2:1). The lubricated granules were compressed at compression force 4000-5000 kg using 9.5 mm flat punch on tableting machine. 10 % starch paste was used as binding agent.

**Drug-Excipient Compatibility Studies:**

Infrared light absorption scanning spectroscopy (IR) studies Infra red spectra of pure drug & mixture of formulation were recorded by dispersion of drug & mixture of formulation in suitable solvent.

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Dispersion of drug and mixture of formulation in suitable solvent was followed by infrared light absorption scanning spectroscopy (IR) studies. Infra red spectra of pure drug and mixture of formulation were recorded on Fourier Transform Infrared Spectrophotometer. A base line correction was made using dried potassium bromide and then the spectra of the dried mixture of drug, formulation mixture and potassium bromide were recorded on FTIR at IISc, Bangalore.

**Table 1. Formulation of colon targeted matrix tablet**

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Tablet Formulation Code</th>
<th>Ingredients (mg/tab)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Containing 10% Gaur gum</td>
</tr>
<tr>
<td>1</td>
<td>Tinidazole</td>
<td>150</td>
</tr>
<tr>
<td>2</td>
<td>Guar gum</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>MCC</td>
<td>232</td>
</tr>
<tr>
<td>4</td>
<td>Purified Talc</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>Magnesium stearate</td>
<td>5</td>
</tr>
</tbody>
</table>

Pre-formulation Parameters:
- 10 % starch paste was used as binding agent
- The best formulation was assessed their accelerated stability with respect to their appearance, hardness, friability, drug contents & drug release characteristics after storing them at 40±2°C / 75±5% RH for 2 month.

**Drug-Excipient Compatibility Studies:**

- Infrared light absorption scanning spectroscopy (IR) studies
- The pure drug and the formulation were subjected to IR studies. This study was carried out to establish that the therapeutically active drug has not undergone any changes. After spectral comparison it was confirmed that no incompatibility reactions takes place between drug components. The pure drug and the formulation mixture were subjected to IR studies. This study was carried out to establish that the therapeutic active drug has not undergone any changes. After spectral comparison it was confirmed that no incompatibility reactions takes place between drug components.

In-vitro Dissolution Studies:

- Disintegration and dissolution studies were performed by using USP Type II Apparatus (Basket type) [Electrolab (ETC-11L) Tablet Dissolution Tester] at 50 rpm for 2 h in 0.1 N HCl (900 ml). Then the dissolution medium was replaced with pH 7.4 phosphate buffer (900 ml) and tested for 3 h as the average transit time of small intestine is 3 h. After 5 h, the dissolution medium was replaced with pH 6.8 phosphate buffer and tested for next 19 h. At the end of time period 10 ml of the sample were taken and analyzed for tinidazole content as described previously. A 10 ml fresh and filtered dissolution medium (buffers) was added to make the volume after each sample withdrawal.

To access the susceptibility of the guar gum to undergo degradation in the presence of colonic bacteria was assayed by continuing the drug release studies in the presence of rat caecal content medium because of the similarity of the microflora of the rat caecal to that of the human colon. The drug release studies were carried out in USP XXIII dissolution rate test apparatus (apparatus 1, 100 rpm, 37°C) with slight modification. A beaker (capacity 150 ml) containing 100 ml of dissolution medium was immersed in the water contained in the 1000 ml vessel, which in turn, was the water bath of the apparatus. The swollen formulations after completing the dissolution study in 0.1 M HCl (2 h) and pH-7.4 phosphate buffer (3 h) were placed in the baskets of the apparatus and immersed in the dissolution medium containing rat caecal content medium. The drug release studies were carried out up to 24 h and 1 ml samples were withdrawn at specified time intervals without a pre- filter and replaced with 1 ml of fresh phosphate buffer. 1 ml of methanol was added in sample and was analyzed for tinidazole content as per above described method.

Stability Studies:
- The best formulation was assessed their accelerated stability with respect to their appearance, hardness, friability, drug contents & drug release characteristics after storing them at 40±2°C / 75±5% RH for 2 month.

RESULTS & DISCUSSION

Pre-formulation Parameters:

Drug-excipient compatibility studies (IR study):
- The pure drug and the formulation were subjected to IR studies. This study was carried out to establish that the therapeutically active drug has not undergone any changes. After spectral comparison it was confirmed that no incompatibility reactions takes place between drug components.
and excipients. IR spectra of pure tinidazole showed characteristic peaks at 3129 cm\(^{-1}\), 2998 cm\(^{-1}\), 2913 cm\(^{-1}\) & 2954 cm\(^{-1}\), which corresponds to aromatic & side chain stretching vibration, at 1430 cm\(^{-1}\) for C=N stretching in imidazole ring, at 982 cm\(^{-1}\), 823 cm\(^{-1}\) for C-H bending vibration of aromatic ring. The entire sample showed the above said changes in the characteristic peaks but peat at 1760 cm\(^{-1}\), 1521 cm\(^{-1}\), 1356 cm\(^{-1}\), 982 cm\(^{-1}\), 1036 cm\(^{-1}\)& 883 cm\(^{-1}\) has non change. These indicate that aromatic, CH\(_3\) & NO\(_2\) functions & aliphatic side chain of drug did not interact with guar gum or excipients present in formulation.

From the studies, angle of repose found to be 28-34° with bulk densities between 0.55-0.66 g/ml & % compressibility 9-16%. Thickness of all the formulations was the acceptable range of 4 mm to 4.5 mm. The average harness of all the tablet formulations lies in the range of 5.5±0.0147 kg/cm\(^{2}\). The average friability of all the formulations lies in the range of 0.145%. Good and uniform drug content (>98) was observed within the batches of different tablet formulation.

**In-vitro dissolution studies:**

The ability of guar gum matrix tablet of tinidazole to remain intact in the physiological environment of stomach and small intestine was assessed by conducting drug release studies under condition mimicking mouth to colon transit. *In vitro* dissolution studies were performed as per the procedure described in methodology section. All the colon targeted matrix tablet formulations of tinidazole
The *in-vitro* dissolution study of conventional marketed product was found to be $F_{MR}^{**}$ 99.59% within 9 h, from this data it was found to be that the conventional marketed product was also failed to retard the drug release in 24 h of study period. From the *in-vitro* dissolution studies it can be discussed that the colon targeted matrix tablet containing 40% guar gum was the best formulation to target the tinidazole to the colon in the treatment of amoebiasis. From the *in-vitro* dissolution studies in the presence of rat caecal content it was found to be that the drug release increased in the presence of 4 % w/v rat caecal content and the colon targeted matrix tablet containing 40% guar gum released 98.62% of tinidazole. It may be due to the presence of colonic bacteria which act on the guar gum & digest it. Therefore released maximum quantity of tinidazole in colon & retard the drug release in the environment of stomach & small intestine.

### Stability studies of colon targeted matrix tablet of tinidazole

#### Table 3 Result of % Drug Content & Morphology of Colon Targeted Matrix Table After The Stability Studies At 40± 2 °C / 75±5 % RH For 2 Month

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Sampling interval</th>
<th>Physical Appearance Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Hardness (kg/cm$^2$)</td>
</tr>
<tr>
<td>GF$_6$</td>
<td>Initial</td>
<td>5.6±0.115</td>
</tr>
<tr>
<td></td>
<td>15 days</td>
<td>5.5±0.152</td>
</tr>
<tr>
<td></td>
<td>30 days</td>
<td>5.0±0.115</td>
</tr>
<tr>
<td></td>
<td>60 day</td>
<td>5.0±0.288</td>
</tr>
</tbody>
</table>

#### Table 4 Result of % Drug Content & Morphology Of Colon Targeted Matrix Table After The Stability Studies At 40± 2 °C / 75±5 % RH For 2 Month

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Sampling interval</th>
<th>Drug content %</th>
<th>Morphology (appearance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GF$_6$</td>
<td>Initial</td>
<td>98.79</td>
<td>——</td>
</tr>
<tr>
<td></td>
<td>1 month</td>
<td>98.77</td>
<td>——</td>
</tr>
<tr>
<td></td>
<td>2 month</td>
<td>98.72</td>
<td>+</td>
</tr>
</tbody>
</table>

| indicates no change in morphology |

+ indicates mild change in morphology (color intensity)

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were evaluated for *in vitro* dissolution studies as per the procedure described in methodology section. The highest *in-vitro* dissolution profile at the end of 24 h was shown by GF$_6$ containing 40% of guar gum (91.21%) followed by GF, containing 50% of guar gum (80.26%), GF$_8$ containing 55% of guar gum (76.21%). The other formulation like, GF$_4$ containing 15% guar gum (96.16%), GF$_3$ containing 10% of guar gum (95.23%), GF$_2$ containing 5% of guar gum (97.98%), GF$_1$ containing 2% of guar gum (98.86%) were failed to target the tinidazole in the colon & these formulation releases the majority of drug within 5 h of study, it may be due to the less proportion of guar gum to retard the drug release.

Figure 5 Cumulative percentage of tinidazole release from colon targeted matrix tablet in the presence of 4 % w/v rat caecal content.

Figure 6 Cumulative percentage of drug release from GF$_6$ with & without 4 % w/v rat caecal content.

Figure-7 Percentage of tinidazole released from GF$_6$ after stability studies.
CONCLUSION
All the colon targeted matrix formulations prepared were evaluated for physicochemical parameters such as appearance, physical properties, drug content and in vitro dissolution studies and stability studies. All the physical characteristics of the formulations like thickness, hardness, friability, drug content, and in vitro dissolution study were found to be well within the limits and official standards. Stability of the tablets in at conditions 40 ±2°C / 75 ±5 % RH, was assessed and observed for appearance, hardness, friability, drug content & in vitro study. From the stability studies it found to be that the formulation was stable at 40 ±2°C / 75 ±5 % RH.
From the in vitro dissolution studies it was found to be that formulation GF1, with 2% guar gum, GF2, with 5% guar gum, GF3, with 10% guar gum & GF4, with 15% guar gum were failed to retard the drug release it might be due to, the formulation released the majority of drug within 5 h in the region of stomach & small intestine. The formulation GF3 containing 20% guar gum was also failed to retard the drug release, GF4 formulation released 97.77 % drug within 12 h and was unable to maintain the drug release through out the study period 24 h. Form that it was found to be that the formulations containing 20 % of guar gum was not target the colon in the form of colon targeted matrix tablet. In vitro release data of marketed product was reveled that; the single dose was unable to target the drug to colon because the marketed product releases the majority of drug within 9 h. Formulation GF8, with 40 % guar gum emerged to be the best one, because it exhibits the best overall general appearance, hardness of 5.5±0.147 Kg/cm2, friability & and a maximum percentage drug released 91.21 without rat caecal content & 98.62 with rat caecal content at the end of 24 h in vitro dissolution studies. In the present, the matrix formulation containing 40% guar gum is most like to target tinidazole to colon without being release significantly in stomach & small intestine.

REFERENCES


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