Formulation and Evaluation of Colon Specific Matrix Tablet of Diethylcarbamazine Citrate

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ABSTRACT

The objective of the present study was to develop colon specific sustained release matrix tablets of an antifilarial drug diethylcarbamazine citrate (DEC), delivered to colon for its effective actions. The colon targeted matrix tablet was prepared by wet granulation technique using different percentage of guar gum as matrix carrier and coated with Eudragit L-100. The novelty in this study was to incorporate guar gum as carrier to retard the drug release in the region of stomach and small intestine. Eight batches of matrix tablet were subjected to various evaluations including the comparison with conventional marketed product. The dissolution study of DEC matrix tablet was in simulated colonic fluids (phosphate buffer pH 6.8) was 94% and in simulated colonic fluids (rat caecal content medium) was 98% after degradation into 2-3 pieces at the end of the 24 h study. The result of the studies showed that colon targeted matrix tablet containing 45% of guar gum was most likely to provide targeting of DEC for local action in the colon. The colon targeted matrix tablet of DEC showed no change either in physical appearance, drug content or in dissolution pattern after storage at 30±2°C/65±5% RH for 2 month. FT-IR spectrum showed no interaction between DEC and guar gum.

Keywords: Colon targeted matrix tablet, diethylcarbamazine citrate, guar gum, rat caecal content.

INTRODUCTION

Helminths are parasitic worms and helminth infections are prevalent globally, one third of world’s population harbours them, but is more common in developing tropical and subtropical countries with poorer personal and environmental hygiene. Anthelmintics are drugs that either kill (vermicide) or expel (vermifuge) infesting helminths1. The choice of drug for each worm infestation was based not only on efficacy, but also on lack of side effects/toxicity, ease of administration (preferably single dose) and low cost. Development of resistance has not been a major problem in the clinical use of anthelmintics2.

The current choice of drugs for worm infestations common in Indian subcontinent are: mebendazole, albendazole, pyrantel pamoate, thiabendazole, diethylcarbamazine, niridazole, praziquantel, ivermectin which are used for round worm (Ascaris lumbricoides), hook worm (Ancylostoma duodenale), thread worm (Enterobius vermiculosis), whip worm, guinea worm, tape worm etc1.

The only effective drug for filariasis is diethylcarbamazine citrate (DEC). This drug should be delivered to colon for its effective action against microfilariae. The administration of this drug in conventional tablet dosage form provides minimal amount of diethylcarbamazine for local action in the colon, still resulting in the relief of filariasis, but with unwanted systemic side effects3,4. The oral route is considered as most convenient for administration of drugs to patients. Oral administration of conventional dosage forms normally dissolves in stomach fluid and gets absorbed from these regions of the gastrointestinal tract. 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 protect from the hostile environment of upper GIT. Dosage forms that deliver drugs into the colon rather than upper GIT prefers number of advantages to the conventional dosage forms5,6.

MATERIALS AND METHODS

Drugs and chemicals

Diethylcarbamazine citrate was received as a gift sample of drug from Shreeji Pharma International, Gujarat, India. Guar gum was received from M/s AIC Enterprises, Bangalore. Magnesium stearate, purified talc, HPMC K 100, citric acid and PEG-4000 were received from S.D. Fine chemicals, Mumbai. Starch, Eudragit RL-100 was received from Mahendra Labs Pvt. Ltd., Bangalore.

Preparation of matrix tablet

Matrix tablet of diethylcarbamazine citrate (DEC) was pre-
prepared by the wet granulation technique using 10% starch paste. HPMC K 100 M was used as diluent and the mixture of talc and magnesium stearate at 2:1 ratio was used as lubricant. The composition of different matrix formulation used in the study containing 10 mg of diethylcarbamazine as shown in Table 1. In the all formulation guar gum was sieved (sieve no. 60) separately and mixed with diethylcarbamazine citrate (sieve no. 100) and HPMC K100 M (sieve no. 60). The powder were blended and granulated with 10% starch paste. The wet mass obtained, then passed through a mesh (100 µm or sieve no. 16) and were lubricated with a mixture of t alc and magnesium stearate (2:1). The lubricated granules were compressed at compression force 4000-5000 kg using 8 mm flat punch on tabletting machine. The tablets were coated with a 10% w/v solution of Eudragit RL-100, using a pan coating equipment. PEG-4000 (1% w/v) was used as a plasticizer. The percent weight increase of each group of formulation of tablets after coating varied between 2.0 ± 0.005% w/w.

Evaluation of granules

Angle of repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:7,9

\[ \tan \theta = \frac{h}{r} \]

Therefore, \[ \theta = \frac{1}{n} \frac{h}{r} \]

Where \[ \theta \] is angle of repose.

\[ h \] = height of the cone in cm.

\[ r \] = radius of the cone base in cm.

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas:7,9

\[ \text{Bulk density} = \frac{\text{weight of the powder}}{\text{bulk volume of the powder}} \]

Compressibility index

\[ \% \text{Carr's index} = \frac{D_t - D_b}{D_t} \times 100 \]

Where, \[ D_t \] is the tapped density of the granules. \[ D_b \] is the bulk density of the granules.

Evaluation of tablets

Thickness

The thickness of six tablets was measured using vernier calipers. The extent to which the thickness of each tablet deviated from ±5% of the standard value was determined.

Hardness

Monsanto hardness tester determined hardness of the tablets. Six tablets from each batch were selected and evaluated, and the average value with standard deviation was recorded.5,10

Friability

Friability of tablets was performed in a Roche friabilator. Ten tablets were weighed together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and re-weighed5,11.

Weight variation test

Uniformity of weight test as described in the IP was followed. Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with the average weight. The percent weight variation test was noted.9,10

Figure 1. Cumulative percentage diethylcarbamazine release from colon targeted matrix tablet.

<table>
<thead>
<tr>
<th>% Cumulative drug release (CDR) of various colon targeted formulations of diethylcarbamazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (h)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>6</td>
</tr>
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<td>8</td>
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<td>20</td>
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<td>22</td>
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<tr>
<td>24</td>
</tr>
</tbody>
</table>

IF1 containing 7.5% of guar gum, IF2 containing 15% of guar gum, IF3 containing 22.5% of guar gum, IF4 containing 30% of guar gum, IF5 containing 37.5% of guar gum, IF6 containing 45% of guar gum, IF7 containing 52.5% of guar gum, IF8 containing 60% of guar gum.
age deviation was calculated and checked for weight variation. Using this procedure weight variation range of all batches of formulations were determined and recorded.

Uniformity of drug content

The matrix tablets were tested for their drug content. Weighed and powdered 20 tablets. Quantity of the powder equivalent to 15 mg of diethylcarbamazine citrate was weighed and dissolved in 20 ml of methanol, shaken well and added sufficient methanol to produced 100 ml. Mixed well and filtered. Diluted 10 ml of the above solution with methanol and further diluted 10 ml of this solution to 100 ml with methanol. The absorbance of resulting solution was measured as per reported method.

**In vitro dissolution Studies**

**In vitro** dissolution study was performed by using USP Type II Apparatus (Basket type) [Electrolab (ETC-11L) Tablet Dissolution Tester] at 100 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 next 3 h. 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 diethylcarbamazine content as per previously described method.

Stability studies

The International Conference of Harmonization (ICH) guidelines titled, “stability testing of New Drug substance and products” (QIA) describes the stability test requirements for drug registration application in the European Union, Japan and the United States of America. ICH specifies the length of study and storage conditions 30°C ± 2°C / 60% ± 5% RH for 2 months.

Statistical analysis

Except dissolution all evaluation parameters were expressed as mean ± standard deviation (S. D.).

**RESULTS AND DISCUSSION**

Matrix tablet of diethylcarbamazine citrate (DEC) were prepared by the wet granulation technique using 10% starch paste. HPMC K 100 M 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 10 mg of diethylcarbamazine is given in Table 1. In the present study, guar gum was added to make the volume after each sample withdrawal.

**In vitro dissolution Studies in the presence of 4% w/v rat caecal content**

To assess the susceptibility of the guar gum to undergo degradation in the presence of colonic bacteria was done by continuing the drug release studies in the presence of rat caecal content medium because of the similarity of the micro flora of the rat caecal to that of the human colon. The drug release studies were carried out in USP dissolution 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 diethylcarbamazine content as per previously described method.

**Table 1. Formulation chart of prepared diethylcarbamazine citrate matrix tablets.**

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Diethyl-carbamazine (mg)</th>
<th>Guar gum (% mg)</th>
<th>HPMC (E50LV) (mg)</th>
<th>Starch (mg)</th>
<th>Citric Acid (mg)</th>
<th>Mg-Stearate (mg)</th>
<th>Talc (mg)</th>
<th>Total Wt (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IF1</td>
<td>10</td>
<td>7.5</td>
<td>18.75</td>
<td>62.5</td>
<td>156.25</td>
<td>25</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>IF2</td>
<td>10</td>
<td>15</td>
<td>37.75</td>
<td>55</td>
<td>137.5</td>
<td>25</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>IF3</td>
<td>10</td>
<td>22.5</td>
<td>56.25</td>
<td>47.5</td>
<td>118.75</td>
<td>25</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>IF4</td>
<td>10</td>
<td>30</td>
<td>75</td>
<td>40</td>
<td>100</td>
<td>25</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>IF5</td>
<td>10</td>
<td>37.5</td>
<td>93.75</td>
<td>32.5</td>
<td>81.25</td>
<td>25</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>IF6</td>
<td>10</td>
<td>45</td>
<td>112.5</td>
<td>25</td>
<td>62.5</td>
<td>25</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>IF7</td>
<td>10</td>
<td>52.5</td>
<td>131.25</td>
<td>17.5</td>
<td>43.75</td>
<td>25</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>IF8</td>
<td>10</td>
<td>60</td>
<td>150</td>
<td>10</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>5</td>
</tr>
</tbody>
</table>
was incorporated at various percentages to retard the drug release in the environment of stomach and small intestine and further coating was done with 10% Eudragit-L 100. The granules were prepared by the method described in the methodology section. The lubricated granules were compressed at compression force 4000-5000 kg using 8 mm flat punch on tabletting machine and then coated using the EudragitSM L-100 solution containing PEG 4000 as plasticizer.

**Micromeritic properties**

The powder blend was evaluated for angle of repose, bulk density and compressibility index. From the studies, angle of repose found to be 26-32° C with bulk densities between 0.61-0.68 g/ml and % compressibility 11-17 %.

**Thickness hardness and friability of tablets**

Thickness of all the formulations was the acceptable range of 4.8 mm to 5.3 mm. The average hardness of all the tablet formulations lies in the range of 5.7 ± 0.0147 kg/cm² the average friability of all the formulations lies around 0.135%.

**Weight variation test**

Average weight of the tablet was 250 mg with weight variation (250 mg ± 5%) (240 to 250 mg). Thus all the formulations were found to be complying with the standards given in IP.

**Uniformity of drug content**

Uniformity of weight test for all formulations was carried out using the procedure described in methodology section and results were shown in Table 2. Good and uniform drug content ( > 98) was observed within the batches of different tablet formulation.

**In vitro dissolution studies**

All the colon targeted matrix tablet formulations of DEC 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 IF6 containing 45 % of guar gum (94.69 %) followed by IF7 containing 52.5 % of guar gum (85.76 %), IF8 containing 60 % of guar gum (75.21 %). The other formulation like, IF4 containing 30 % guar gum (96.89 %), IF3 containing 22.5 % of guar gum (97.41 %), IF2 containing 15 % of guar gum (96.45 %), IF1 containing 7.5% of guar gum (98.41 %) were failed to target the diethylcarbamazone into the colon and these formulation releases the majority of drug within 10 h of study, it may be due to the less proportion of guar gum to retard the drug release.

The in vitro dissolution study of conventional marketed product was found to be $F_{avg}$ 98.29 % 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 45% guar gum was the best formulation to target the DEC to the colon in the treatment of filariasis. 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 45% guar gum released 98.62% of DEC. It may be due to the presence of colonic bacteria which act on the guar gum and digest it. Therefore released maximum quantity of diethylcarbamazine citrate in colon and retard the drug release in the environment of stomach and small intestine.

**Stability studies**

The selected formulations were subjected to the accelerated stability at 30 ± 2 °C / 65 ± 5 % RH for 2 months and evaluated for their appearance, hardness, friability, drug content and in vitro dissolution studies. There were no significant variations in the appearance, hardness, friability, drug content and in-vitro dissolution studies.

**CONCLUSION**

The main objective of this study was the development of a colon targeted matrix tablet formulation of diethylcarbamazine citrate, by wet granulation technique using various proportion of guar gum as polymer, further coating was done using Eudragit-L 100. It was found that the formulation liberation in the stomach was prevented by enteric coating but after gastric emptying drug release was adjusted by incorporation of citric acid, the tablet is likely to remain entire for longer period. In this way drug release at the end of the small intestine might be prevented even through pH levels exceeding 7. In the colon the formulation can disintegrate into granules. These can then distribute themselves throughout the colon. 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. The
susceptibility of the matrix tablets to the enzymatic action of colonic bacteria was assessed by performing the drug release studies in medium containing rat caecal material (4%). In vitro release data of marketed product was revealed 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 IF6 with 45% 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 release 94.69% without rat caecal content and 98.62% with rat caecal content at the end of 24 h in vitro dissolution studies. In the present study, the matrix formulation containing 45% guar gum is most likely to target diethylcarbamazine citrate to colon without being released significantly in stomach and small intestine.

REFERENCES


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