ABSTRACT

The aim of the current study was to investigate the in-vitro performance of compressed coated tablet of Budesonide. A novel colon targeted tablet formulation was developed by press coating of Budesonide with guar gum and Eudragit S-100 as barrier layer. The entire device was enteric coated so that variability in gastric emptying time can be overcome and a colon specific release can be achieved. Different ratios of polymers were selected to achieve suitable lag time for the treatment of Crohn’s disease and ulcerative colitis. In-vitro release studies for prepared tablets were carried out for 2 h in 1.2 pH phosphate buffer, 3 h in pH 6.8 phosphate buffer and 6 h in simulated colonic fluid. In vitro studies revealed that the tablet coated with guar gum and Eudragit S-100 have limited drug release in stomach and small intestinal environment and released maximum amount of drug in the colonic environment. Colon specific release has been achieved from tablet of F5 formulation (0:100) which not given release in stomach and small intestine and about 98.87% drug release in the colon.

MATERIAL AND METHODS:

Material used for compression coated tablets like Microcrystalline cellulose, Sodium Starch Glycolate, Magnesium stearate were purchased from Lobachem, and used as inner core tablet excipient, Eudragit S100 and Guar gum also purchased from lobachem and used as outer coating material.

1) Compatibility study:

10 vials were taken and it is divided into 2 sets each set contain 5 vials in each vial 5mg of the drug and 5mg of the excipient were added except magnesium stearate which was added in 1:20 ratio means 20mg drug and 1mg magnesium stearate. All parameters like initial appearance and other recorded. Individual IR graph were taken before placing the ingredient and drug into the vials and these vials were kept for 14 days for 55°C in duration of 14 days all the vials were observed for any colour change, gas formation and precipitation lastly its IR was studied.

2) Assay of Budesonide Powder:

Weigh 2.5mg equivalent weight of the Budesonide powder. Take it in a 25ml volumetric flask. 5 ml of hydrotrropic solution which contain 45% urea and 5% sodium citrate were added in to the flask. Shake for 10 min. and make up volume up to the mark. Filter through the whatman filter paper. Filtered extract were diluted with distilled water to form serial dilutions like 5, 10, 15, 20, 25, 30 and absorbances were taken at 244.8 nm.

3) Evaluation of precompression parameter for compression coated tablet:

The powder mixture of all batches were evaluated for bulk density, tapped density, Carr’s index and Hausner ratio and results for flow properties were concluded in the table no.3.

INTRODUCTION:

Site-specific delivery of drugs to the site of action has the potential to reduce side effects and to increase pharmacological response. One of the seemingly interesting areas to target drugs through oral route is the colon. Various systems have been developed for colon-specific drug delivery: covalent linkage of a drug with a carrier, coating with pH-sensitive polymers, time-dependent release systems, and enzymatically controlled delivery systems. Enteric-coated systems are the most commonly used for colon drug delivery. The drawback of the time-dependent release system is its inability to sense any variation in the upper gastrointestinal tract transit time; besides, any variation in gastric emptying time may lead to drug release in the small intestine before arrival to the colon. To overcome this drawback of premature release of drug from dosage form into stomach and small intestine eudragit S100 compression coated tablet was prepared because eudragit S100 degrade only above pH 7 and thus premature release is avoided due to compression coating.2,3

Budesonide is a potent corticosteroid that has important implications in the pharmacotherapy of inflammatory bowel disease, especially in the treatment of ulcerative colitis and Crohn’s disease. BUD is approximately twice as active as beclomethasone dipropionate, and it is over 1,000 times more active than either prednisolone or hydrocortisone in inducing intracutaneous vaso-constriction (as a marker of anti-inflammatory activity). BUD is commercially available in the market in the form of enteric-coated preparations mainly for the treatment of small intestine active Crohn’s disease. However, these products, similar to other available site specific dosage forms, are not sufficiently selective to treat colonic inflammatory bowel disease. It was found that less than 5% of the drug was available beyond the ileum and cecum, and therefore, colonic delivery still needs to be optimized by a more reliable colon-specific system. Previous workers have developed BUD microparticles for colon delivery. However, being relatively complex systems, their large-scale manufacturing requires a lot of technological advancement and skills. So, an attempt was made to formulate compression-coated tablets, which could be formulated easily, using the usual tableting techniques2,3.
4) Preparation of tablet:

A) Preparation of core tablet:
All the ingredient of core tablet like Budesonide 9mg, Sodium starch glycolate 2.5, Magnesium stearate 7mg, Microcrystalline cellulose 61.5mg were weighed and it is directly compressed by using 6mm flat punch. The formula for core tablet is given in table no.111,12,13.

Table 1 Formula for core tablet

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide</td>
<td>9</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>2.5</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>7</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>61.5</td>
</tr>
<tr>
<td>Total weight</td>
<td>80</td>
</tr>
</tbody>
</table>

B) Preparation of compression coated tablet:
After preparation of the core tablet it was compressed coated with outer coating layer by using 8mm punch the material used for the outer coating layer were Eudragit S100 and Guar gum. Firstly the half quantity of outer layer was weighed and it is placed at the bottom then core tablet was placed at the middle and again remaining outer layer was placed and it was directly compressed with 8mm punch and thus compression coated tablet was prepared. The formula for outer coating layer is given in table no.214,15,16.

Table 2 Formula for outer coating layer

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit, Guar gum, Budesonide</td>
<td>80:20</td>
<td>100:0</td>
<td>80:20</td>
<td>100:0</td>
<td>80:20</td>
<td>100:0</td>
</tr>
<tr>
<td>Total weight</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
</tbody>
</table>

5) Evaluation of the compression coated tablet:
Compression coated tablet of budesonide was evaluated for friability testing, weight variation test, hardnesstest, angle of repose, and results were concluded in table no.417,18.

6) In vitro dissolution testing of budesonide compression coated tablet:
Dissolution testing was carried out by using usp type II apparatus (Electrolab). Dissolution medium used for the testing were pH 1.2, 6.8, 7.4 phosphate buffer, compression coated tablet was placed in pH 1.2 phosphate buffer for 2hrs because gastric emptying time is 2hrs, 5ml sample was pipette out specific time interval (1hr), then that medium was replaced with pH 6.8 phosphate buffer and testing carried out for 3hrs because intestinal emptying time is 3hrs, after that pH 6.8 was replaced by using pH 7.4 phosphate buffer and testing carried out for about 12hrs and drug release was checked in particular medium by using uv at particular drug (Budesonide) wavelength 246nm. Dissolution test was performed and results were recorded in table no.519,20.

7) In vitro dissolution testing in presence of rat caecal content:
Dissolution testing of budesonide compression coated tablet was carried out in pH phosphate buffer 1.2, 6.8, 7.4 which contain rat caecal content. 4% of rat caecal content was added in dissolution medium and dissolution testing was carried out For pH 1.2, 2 hrs; for pH 6.8, 3 hrs; and for pH 7.4, upto 6hrs. 5ml sample were removed at 1hr time interval and it was tested for its absorbances by using UV spectrophotometer (Shimadzu 1800) and results were note down in table no.6.

8) Assay of the budesonide tablet:
Twenty tablet of Budesonide weighed and finely powdered. Powder equivalent to the 2.5mg of the budesonide was taken in 25ml of volumetric flask. 5ml of mixed hydrotrropic solution containing 45% urea and 5% sodium citrate was added. Shake for 10min. Make up volume up to the mark. Filter extract, dilute with distilled water. Take absorbances at 244.8nm against reagent blank and drug content was calculated.

9) Stability testing of budesonide compression coated tablet:
The stability studies were carried out according to ICH to asses the drug formulation stability. Optimized F formulation was sealed in aluminum packaging laminated with polyethylene. Samples were kept at 40°C and 75% RH for 3months. At the end of the study period, the formulation was observed for change in physical appearance, color, drug content and drug release characteristics. After 3months budesonide tablet is also evaluated for stability by using IR (ALPHA BRUKER) for that firstly the individual IR of Eudragit, Guar gum, Budesonide were taken and then IR of compression coated tablet was taken by crushing compression coated tablet in mortar with the help of pestle and results were concluded from that IR graph, also the DSC was performed for checking the stability of compound. The graphs of IR given in figure number 3 and 4 for DSC in figure number 5 and 619,20.

10) In vitro release kinetic of the budesonide compression coated tablet:
Data obtained from in vitro release studies were fitted to various kinetic equations to find out the mechanism of budesonide compression coated tablets. All results are presented in table no.7. Release kinetic study was done by using kinetics equation of Higuchi’s square root method which gave value of cumulative percent of drug release vs. square root of time. When cumulative percentage drug released vs. time is plotted then it is zero order and if log cumulative percentage of the drug released vs. log of time is plotted then it gives first order release21.

RESULT AND DISCUSSION:

1) Assay budesonide powder:
Assay of budesonide powder was performed by uv spectrophotometer (Schimadzu 1800) and percentage purity was found to be 98.83% and it complies with Indian Pharmacopoeia 2010 limit( not less than 98% and not more than 102%).

2) Evaluation of precompression parameter of budesonide compression coated tablet:
Table no.3 shows the values of Carr’s index, Hausner ratio, Bulk density and Tapped density. Carr’s index for powder blends of F1, F2 were in the range of 18-21 indicating fair flow. Carr’s index of F3, F4 and F6 were in the range of 12-16 indicating good flow and F3, F5 indicate excellent flow. Hausner ratio of F5 in the range of 1-1.11 indicate excellent flow of powder blend, while F3, F4 and F6 were in the range of 1.12-1.18 indicating good flow while F1 shows fair flow of powder.

Table 3 Evaluation of precompression parameter of budesonide compression coated tablet:

<table>
<thead>
<tr>
<th>Ratio of guar gum: Eudragit (G:E) &amp; formulation code</th>
<th>Bulk density</th>
<th>Tapped density</th>
<th>Carr’s index</th>
<th>Hausner ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>100:0 (F1)</td>
<td>0.71</td>
<td>0.89</td>
<td>20.54</td>
<td>1.25</td>
</tr>
<tr>
<td>80:20 (F2)</td>
<td>0.67</td>
<td>0.83</td>
<td>19.67</td>
<td>1.23</td>
</tr>
<tr>
<td>60:40 (F3)</td>
<td>0.55</td>
<td>0.62</td>
<td>12</td>
<td>1.12</td>
</tr>
<tr>
<td>50:50 (F3)</td>
<td>0.55</td>
<td>0.62</td>
<td>12</td>
<td>1.12</td>
</tr>
<tr>
<td>40:60 (F3)</td>
<td>0.45</td>
<td>0.52</td>
<td>13.46</td>
<td>1.15</td>
</tr>
<tr>
<td>30:70 (F3)</td>
<td>0.45</td>
<td>0.55</td>
<td>10</td>
<td>1.11</td>
</tr>
<tr>
<td>20:80 (F4)</td>
<td>0.45</td>
<td>0.52</td>
<td>13.46</td>
<td>1.15</td>
</tr>
<tr>
<td>10:90 (F4)</td>
<td>0.45</td>
<td>0.55</td>
<td>10</td>
<td>1.11</td>
</tr>
<tr>
<td>0:100 (F5)</td>
<td>0.45</td>
<td>0.55</td>
<td>10</td>
<td>1.11</td>
</tr>
<tr>
<td>40:60 (F6)</td>
<td>0.64</td>
<td>0.75</td>
<td>15.66</td>
<td>1.17</td>
</tr>
</tbody>
</table>
3) Physical characterization of compression coated tablet:
The coat formulations containing various proportions of guar and eudragit. Physical properties of compression coated formulations were shown in table 4. The thickness range of compression coated formulations were 8.005mm to 8.007mm. The hardness of the compression coated tablet containing only guar gum was 4kg/cm² and combination of guar gum and eudragit in the range of 5 to 6 kg/cm², whereas for total eudragit coated tablet it was 6 kg/cm². Friability of all batches from F1 to F6 were below 1%. Angel of repose of the powder blend were in the range of 20.30 to 24.70 which shows that powder has excellent flow properties.

Table. 4 Physical characterization of the compression coated tablet like hardness, friability and weight variation:

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>% Ratio of Guar gum : Eudragit</th>
<th>Hardness Kg/cm²</th>
<th>Friability (%)</th>
<th>Weight Variation (%)</th>
<th>Angel of Repose</th>
<th>Diameter of tablet (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>100:0</td>
<td>4</td>
<td>0.909</td>
<td>0.133</td>
<td>24.70</td>
<td>8.005</td>
</tr>
<tr>
<td>F2</td>
<td>80:20</td>
<td>5</td>
<td>0.74</td>
<td>0.134</td>
<td>22.29</td>
<td>8.005</td>
</tr>
<tr>
<td>F3</td>
<td>50:50</td>
<td>6</td>
<td>0.69</td>
<td>0.134</td>
<td>22.78</td>
<td>8.007</td>
</tr>
<tr>
<td>F4</td>
<td>20:80</td>
<td>5</td>
<td>0.63</td>
<td>0.067</td>
<td>21.30</td>
<td>8.006</td>
</tr>
<tr>
<td>F5</td>
<td>0:100</td>
<td>6</td>
<td>0.60</td>
<td>0.067</td>
<td>20.30</td>
<td>8.007</td>
</tr>
<tr>
<td>F6</td>
<td>40:60</td>
<td>6</td>
<td>0.69</td>
<td>0.134</td>
<td>22.78</td>
<td>8.006</td>
</tr>
</tbody>
</table>

4) In vitro dissolution testing without human fecal matter:
Dissolution testing was carried out in phosphate buffer 1.2 for 2hrs, in 6.8 for 3hrs, in 7.4 for about 7 hrs and 5ml sample was pipette out at 1hr time interval and absorbances was taken by uv spectrophotometer. From in vitro dissolution testing it was found that out of six batches 3 batches were given less release in the pH 1.2 and in pH 6.8. Out of six batches F5 and F6 were the best batches, F5 batch given no release in the 1.2 pH and only 2.15% release in the small intestine thus it gives maximum amount of the drug to the colon while batch F4 also given very less release in stomach and small intestine. The release of batch F4 in stomach was 1.89% while in small intestine was 5.99% which is also permissible for colonic drug delivery system so these batches F5 and F4 were carried out for dissolution in presence of human fecal matter and drug release were checked. The percentage drug release of the in vitro dissolution without enzyme is given in table no.5. The graphical representation of drug release for batch F4 and F5 given in fig.1.

5) In vitro dissolution testing by using rat caecal content:
For this dissolution testing freshly prepared rat caecal content was used because it contain various colonic enzyme. 4% of rat caecal content was added for 900ml of pH 1.2, 6.8, 7.4 phosphate buffer respectively. Upon addition of rat caecal content drug release of batch F5 was 98.87% (Table no.6). This change in drug release of batch F5 is not due to enzymes it is due to less

6) Assay of budesonide compression coated tablet:
Assay of budesonide tablet was performed by using UV Spectrophotometer (Shimadzu 1800). Each tablet of budesonide was contain about 9 mg of budesonide after doing assay it was observed that budesonide compression coated tablet contain about 98.83% of the drug which is shows that tablet contain right dose of budesonide in compression coated tablet.

7) In vitro drug release kinetic of budesonide compression coated tablet:
The results of various kinetics models of budesonide compression coated tablets are shown in table 7. The results showed that all formulations best fitted with zero order kinetics, as they contain highest regression coefficient values (0.9879 to 0.9859).

Table no.7 showing in vitro drug release kinetics of budesonide compression tablet

<table>
<thead>
<tr>
<th>Guar gum: Code</th>
<th>Eudragit</th>
<th>Zero order</th>
<th>1st order</th>
<th>Higuchi model</th>
<th>Korsmeyer peppas model</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>100.0</td>
<td>0.9837</td>
<td>0.8518</td>
<td>0.9008</td>
<td>0.8305</td>
</tr>
<tr>
<td>F2</td>
<td>80.20</td>
<td>0.9859</td>
<td>0.8729</td>
<td>0.9550</td>
<td>0.8246</td>
</tr>
<tr>
<td>F3</td>
<td>50.50</td>
<td>0.8869</td>
<td>0.8060</td>
<td>0.8638</td>
<td>0.8150</td>
</tr>
<tr>
<td>F4</td>
<td>20.80</td>
<td>0.9065</td>
<td>0.8332</td>
<td>0.8616</td>
<td>0.8111</td>
</tr>
<tr>
<td>F5</td>
<td>0.100</td>
<td>0.8789</td>
<td>0.8367</td>
<td>0.7853</td>
<td>0.6751</td>
</tr>
<tr>
<td>F6</td>
<td>40.60</td>
<td>0.9383</td>
<td>0.8921</td>
<td>0.9008</td>
<td>0.8338</td>
</tr>
</tbody>
</table>
8) Stability testing of budesonide compression coated tablet:

Fig no.3 showing FTIR spectra of pure Budesonide drug.

Fig no.4 showing FTIR spectra of budesonide compression coated tablet.

Figure 5 showing DSC of pure budesonide drug.
The optimized batch F5 were studied for 3 months. At regular time intervals the tablets were tested for physicochemical properties and in vitro dissolution studies. The result shows the average drug content was 98.83% for F5 of labeled claim and there was no significant changes in vitro dissolution studies, IR studies and DSC studies. From figure 3, 4, 5, 6 it was concluded that the batch F5 is stable batch after 3 months also.

9) CONCLUSION
Based on the drug released in the target site (colon), a blend of Guar gum : EUD S100 in percent ratio 0:100% were considered as optimum batch( batch F5 ) because 0:100 ratio batch given 98.87% drug release in colon and no release in the stomach and small intestine hence it is the batch which given efficient colon targeting.

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