FORMULATION AND EVALUATION OF COLON TARGETED MESALAMINE MATRIX TABLET

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ABSTRACT
The colon is a site where both local and systemic delivery of drugs can take place. Systemic delivery is low but local delivery allows topical treatment of inflammatory bowel disease (IBD). However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects. The aim of the present research work was to develop sustained release matrix formulation of mesalamine targeted to colon by using both hydrophilic and hydrophobic polymers and in-vitro drug release study. Matrix tablets were prepared by direct compression method using different concentration of Hydroxypropylmethylcellulose (HPMC) and Ethyl Cellulose (EC). Prepared formulations were subjected to various studies like hardness, friability, thickness, % drug content, weight variation etc. Tablets were subjected to in-vitro drug release in 0.1 N HCl (pH 1.2), followed by phosphate buffer (pH 6.8). In-vitro drug release data fitting to Higuchi and Korysmeyer-Peppas equation indicated that diffusion along with erosion could be the mechanism of drug release. It was observed that combination of both the polymers exhibited the best release profile and able to sustain the drug release for prolong period of time. The test batch comparison analysis was confirmed that the combination of both hydrophilic and hydrophobic polymers successfully employed for formulating the sustained release colon targeted matrix tablets of mesalamine.

KEYWORDS : Mesalamine, Diffusion, Erosion, Inflammatory bowel disease, HPMC, EC.

INTRODUCTION
An appropriately designed controlled release drug delivery system can be major advance towards solving problems concerning targeting drug to specific organ or tissue and controlling the rate of drug delivery to the target tissue. Matrix
tablet are an interesting option when developing an oral controlled release formulation. The present study focuses on oral controlled release polymer dosage forms and type of various polymers used to formulate matrix tablets. Conventional dosage form release the drug instantaneously and showing large distribution to all organs but in certain disease or disorder there is need to have more drug concentration at specific site and the problem in conventional dosage form is drugs may distributed to all parts, least concentration reaches to required site along with some drug damage to unintentional organ or body tissue. So there is need to target the drug to specific site.

Colon are concerned with number of diseases like IBD, colon cancer etc. The term inflammatory bowel disease (IBD) covers a group of disorders in which the intestines become inflamed (red and swollen). Two major types of IBD are described: ulcerative colitis and corhn’s disease. As the name suggest, ulcerative colitis is limited to the colon (large intestine). Although disease can involve any part of Crohn’s the gastrointestinal tract from the mouth to the anus, it most commonly affects the small intestine and/or the colon.
Both ulcerative colitis and Crohn's disease usually run a waxing and waning course in the intensity and severity illness. When there is severe inflammation, the disease is considered to be in an active stage, and the person experiences a flare-up of the condition.

Colon targeted matrix tablet is one controlled release dosage form, which release the drug in continuous manner at colon. The release of drug may be both dissolution controlled as well as diffusion controlled maintaining therapeutic blood or tissue levels at of the drug for extended period of time with minimized local or systemic adverse effects.

It is very challenging task to prepare such dosage form which could be target the colon. In this study the active drug Mesalamine or5-ASA compound, is an anti-inflammatory drug used to
treat inflammation of the digestive tract (Crohn’s disease) and mild to moderate Ulcerative Colitis. Mesalamine undergoes extensive and highly variable hepatic first-pass metabolism following oral administration, with a reported systemic oral bioavailability between 20% and 30%. Mesalamine has half-life of 5 hours so patients are routinely asked to take Mesalamine for several times in a day. Such frequent drug administration may reduce patient’s compliance and therapeutic efficacy. The objective of the present study was to develop sustained release matrix formulations of Mesalamine and to examine the effects of both hydrophilic and hydrophobic polymers on in-vitro drug release. In the present study, Mesalamine matrix formulations were prepared by using hydrophilic polymer, HPMC and hydrophobic polymer, EC alone and in combination to study the release kinetics and find out the effects of both the polymers and their combinations.

MATERIALS AND METHODS

Materials

Mesalamine was a gift sample from Therdose Pharma Pvt. Ltd, Hyderabad. HPMC, Ethyl cellulose, Microcrystalline Cellulose, Magnesium Stearate and Talc, other materials and solvents used were of analytical grade. In vitro analysis of the prepared tablets was carried out as per the requirements of matrix tablets as specified in official pharmacopeia.

Preparation of tablets:

All the formulations were prepared by direct compression method. The drug (100 mg/tablet) and other excipients used in the formulations passed through a No.60 sieve prior to compression method. The drug (100 mg/tablet) and other excipients used in the formulations passed through a No. 60 sieve prior to compression. Powder blends were prepared using a cone mixer for 15 min. Then talc was added and mixed for another 5 min. The amount of polymers and other ingredients are given in Table-1. The required quantity of the ingredients for preparing the sustained release formulations were compressed using a rotator punch tablet machine equipped with 8 mm circular, flat and plain punches. The batch size of each formulation was 50 tablets. All formulation data are mentioned in table no.1.

Table No.01 Formulation data of mesalamine matrix tablet

<table>
<thead>
<tr>
<th>Formulation Test Batch</th>
<th>Mesalamine (mg)</th>
<th>HPMC (mg)</th>
<th>EC (mg)</th>
<th>MCC (mg)</th>
<th>Talc (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>100</td>
<td>20</td>
<td>-</td>
<td>125</td>
<td>5</td>
</tr>
<tr>
<td>F2</td>
<td>100</td>
<td>40</td>
<td>-</td>
<td>105</td>
<td>5</td>
</tr>
<tr>
<td>F3</td>
<td>100</td>
<td>60</td>
<td>-</td>
<td>85</td>
<td>5</td>
</tr>
<tr>
<td>F4</td>
<td>100</td>
<td>-</td>
<td>20</td>
<td>125</td>
<td>5</td>
</tr>
<tr>
<td>F5</td>
<td>100</td>
<td>-</td>
<td>40</td>
<td>105</td>
<td>5</td>
</tr>
<tr>
<td>F6</td>
<td>100</td>
<td>-</td>
<td>60</td>
<td>85</td>
<td>5</td>
</tr>
<tr>
<td>F7</td>
<td>100</td>
<td>20</td>
<td>20</td>
<td>105</td>
<td>5</td>
</tr>
<tr>
<td>F8</td>
<td>100</td>
<td>40</td>
<td>20</td>
<td>85</td>
<td>5</td>
</tr>
<tr>
<td>F9</td>
<td>100</td>
<td>60</td>
<td>20</td>
<td>65</td>
<td>5</td>
</tr>
</tbody>
</table>

EVALUATION/QUALITY CONTROL TEST

The quality control tests for the matrix tablets, such as hardness, friability, weight variation etc. were determined using reported procedure. The tablet crushing strength was tested by commonly used Pfizer tablet hardness tester. A tablet was placed between the anvils and the crushing strength, which causes the tablet to break was recorded. The control limit is (4 to 5 kg/cm).

Friability was determined by first weighing tablets equivalent to 6.5g after deducting and

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placing them in a Roche® friabilator (Electro lab Pvt. Ltd., India), which was rotated for 4 min at 25 rpm. After de-dusting, the total remaining mass of the tablets was recorded and the percent friability was calculated.

Weight variation was determined by weighing 20 tablets individually, the average weight was calculated and the percent variation of each tablet from the average weight of tablet was calculated.

Disintegration time was determined using the USP disintegration apparatus in 0.1NHCl and Phosphate buffer pH 6.8 maintaining the temperature at 37 ± 2°C. Not a single tablet has disintegrated with two hours in 0.1N HCl, But not a single tablet has remain intact after one hours pH 6.8 phosphate buffer.

Drug release profile was evaluated in vitro using a dissolution test apparatus. The USP XIII Type II (paddle type) method was selected to perform the dissolution profile of mesalamine. The dissolution for six tablets was conducted for 2hrs in 0.1N HCl and later 10hrs in phosphate buffer pH 6.8. The temperature was maintained at 37 ± 0.5°C and a constant paddle rotation speed of 100 rpm. Samples (5 ml) were withdrawn at regular intervals and filtered. The samples were analyzed by UV-spectrophotometer at wavelength 220 nm. The thickness of the tablets was determined using a digital screw gauge (West port, Canada). Five tablets from each batch were used, and average values were calculated (Table 2). All values are mentioned in table no 2.

Table. No.02 Evaluation data of mesalamine matrix tablet showing all parameter in comparative form

<table>
<thead>
<tr>
<th>Test Batch Formulation</th>
<th>Thickness (mm)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Weight Variation (%)</th>
<th>% Drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>7.88</td>
<td>8.6</td>
<td>0.5</td>
<td>2.51</td>
<td>92.82</td>
</tr>
<tr>
<td>F2</td>
<td>7.89</td>
<td>8.4</td>
<td>1.26</td>
<td>2.47</td>
<td>93.48</td>
</tr>
<tr>
<td>F3</td>
<td>7.88</td>
<td>8.5</td>
<td>0.6</td>
<td>1.92</td>
<td>96.16</td>
</tr>
<tr>
<td>F4</td>
<td>7.86</td>
<td>8.7</td>
<td>1.5</td>
<td>2.15</td>
<td>98.74</td>
</tr>
<tr>
<td>F5</td>
<td>7.87</td>
<td>8.6</td>
<td>0.9</td>
<td>1.25</td>
<td>96.38</td>
</tr>
<tr>
<td>F6</td>
<td>7.89</td>
<td>8.4</td>
<td>0.5</td>
<td>1.28</td>
<td>95.95</td>
</tr>
<tr>
<td>F7</td>
<td>7.90</td>
<td>8.9</td>
<td>0.7</td>
<td>1.34</td>
<td>97.89</td>
</tr>
<tr>
<td>F8</td>
<td>7.87</td>
<td>8.5</td>
<td>0.41</td>
<td>2.04</td>
<td>99.24</td>
</tr>
<tr>
<td>F9</td>
<td>7.86</td>
<td>8.7</td>
<td>0.8</td>
<td>1.37</td>
<td>86.38</td>
</tr>
</tbody>
</table>

Analysis of release profiles
The rate and mechanism of release of mesalamine from the prepared matrix tablets were analyzed by kinetic models are given in table no.3

Table no: 03: Kinetic model describing equation and R² value

<table>
<thead>
<tr>
<th>Kinetic Model</th>
<th>Regression Co-efficient value and Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higuchi model</td>
<td>y = 44.368x - 64.345</td>
</tr>
<tr>
<td></td>
<td>R² = 0.9731</td>
</tr>
<tr>
<td>Hixconcrowell cube method</td>
<td>y = 0.2865x + 5.4385</td>
</tr>
<tr>
<td></td>
<td>R² = 0.85</td>
</tr>
<tr>
<td>Korysmeyer-Peppas model</td>
<td>y = 1.5559x + 0.347</td>
</tr>
<tr>
<td></td>
<td>R² = 0.9852</td>
</tr>
</tbody>
</table>

RESULT AND DISCUSSION
Physical characterization of the tablets:
All the formulations were prepared according to the formula given in Table 1. The prepared matrix tablets were evaluated for various physical properties as indicated in Table no.2. All the batches were produced under similar conditions to avoid processing variables. All the formulations available online on www.ijprd.com
were evaluated for various physical Parameters such as weight variation, thickness, hardness, friability and drug content. Hardness of tablets ranged from 8.4 to 8.9 kg/cm², thickness of tablets were found within the range of 7.86 to 7.90 mm. The percentage friability of all the formulations was in between 0.41 to 1.5 percent. The values of hardness test and percent friability indicates good handling property of prepared tablets. The drug content uniformity in the tablets was within the range from 86 to 99 percent.

**In-vitro drug release studies:**

The in vitro drug release study was shown from different kinetic model. Result of kinetic model suggests that their significant difference among test result obtained. It was observed that the drug release was faster from formulations containing hydrophobic polymer ethyl cellulose as compared to hydrophilic HPMC polymer. Since ethyl cellulose is a hydrophobic polymer, it should restrict the penetration of medium inside the matrix and also restrict the formation of gel layer around the matrix as compared to the hydrophilic HPMC. But the concentration used for the matrix formation was not optimum resulting in thin matrix formation which allowed the drug leakage up to the first two hours. When the polymer concentration was increase from 10 to 30% the drug release rate was found to decrease in case of both the polymers. This is due to the reason that the swelling degree is less because of higher concentration of polymers. Formulation F1 and F4 containing 10% HPMC and 10% EC individually were able to sustain the drug release for 8 and 5 hours respectively (92.82% for HPMC at 8 hours and 98.74% for EC at 5 hours in GI Tract). In case of formulation F2, F3 containing 20% and 30% HPMC showed 93.48% and 96.16% drug released in 9 hours and 9 hours respectively. This again, is due to the hydrophilic nature of HPMC which extends the drug release due to formation of gel layer around the formulation.

In case of formulation F5, F6 containing 20% and 30% EC showed 96.38% and 95.95% drug released in 6 hours and 6 hours respectively. This again, is due to the hydrophobic nature of EC which restricts the formation of gel layer around the matrix formulation and retarded drug release from the matrix.

In case of formulation F7, F8, F9 containing 10% constant concentration of EC along with increasing concentration of HPMC 10%, 20%, 30% respectively showed 97.89%, 99.24%, 86.38%. The combination of both hydrophobic polymer Ethyl cellulose and hydrophilic polymer HPMC extended the release up to 12 hrs. The matrix nature of EC along with the swelling property of HPMC gave the tablet good retarding nature. With increase in concentration of HPMC the swelling nature reduced and the release was retarded to a higher extent.

Hence F8 formulation was selected as the optimum concentration which showed 99.24% of drug release up to 12 hrs.

In case of formulation F8, where combination of both the hydrophilic and hydrophobic polymers were present at a different concentration (10% EC was incorporated with 20% HPMC), was able to release the drug for 12 hours (99% drug released in 12 hours). This may occur due to presence of both hydrophilic and hydrophobic polymer which allows little swelling but did not allow rapid diffusion of the drug from the matrix.

The release profiles of the various formulations were plotted in Graph no-1,2,3 below.
The release kinetic data for all the formulations is shown in Table no.3. The kinetic data of all the formulation showed good fit in Higuchi model equation and Korsmeyer-Peppas model equation which indicated the combined effect of diffusion.
and erosion mechanism for controlled drug release from the swellable polymer. The $R^2$ value of Higuchi model and Korsmeyer-Peppas model are nearer to 1. Hence test batch F8 produces desired release pattern which is responsible for maintaining concentration at colon.

The release kinetic data of the optimum formulation was plotted in Graph no-4, 5, 6 below.

**Graph no: 04:** % drug release v/s square root of time

![Graph showing % drug release vs square root of time](image)

Hixson Crowell cube Model

**Graph no: 05:** cube root of % drug remaining v/s time (min)

![Graph showing cube root of % drug remaining vs time](image)

Korsmeyer-Peppas Model

**Graph no: 06:** log % drug release v/s log time

![Graph showing log % drug release vs log time](image)
CONCLUSION
Results of the present research work demonstrate that the combination of both hydrophilic and hydrophobic polymers successfully employed for formulating the colon release matrix tablets of mesalamine. It is observed that 10% of EC polymer and 20% of HPMC polymer in combination was able to produce desire formulation which release more than 99% drug in 12 hours. The mechanism of drug release was observed the combined effect of diffusion and erosion for controlled drug release. So, combination of both hydrophilic and hydrophobic polymer was suitable to produce the colon targeted matrix tablet rather than the using a single type of polymer.

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