Formulation and Evaluation of Enteric Coated Matrix Tablets of Mesalamine for Inflammatory Bowel Disease

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INTRODUCTION

The importance of pharmaceuticals that are specifically absorbed from the colon region has mostly been supplied by the colon specific drug delivery system, which prevents degradation in the upper gastrointestinal tract (GIT). The release of drugs at this location will assure the greatest therapeutic benefit¹–³. Colon-targeted delivery systems are useful for treating localised colonic disorders such as Crohn’s disease, ulcerative colitis, and constipation, which are best addressed by drug delivery to the colon⁴. The medicine should be protected from absorption in the stomach and small intestine by the colon-specific delivery system, preventing a fast commencement of drug release upon entering the colon’s less hostile environment. To deliver anti-inflammatory agents to the sites of inflammation, various drug delivery approaches have been developed, including pH-sensitive system, time-dependent system, pro-drugs, and microflora-activated system, and thus systemic drug absorption should be reduced, as this leads to unwanted systemic side effects⁵–⁷. The pH-sensitive system and the time-dependent system are the most commonly utilised systems for colon-specific medication delivery⁸–¹⁰. Polysaccharides are monosaccharide polymers with a variety of qualities. They are cheap and come in a variety of forms. Several polysaccharides, such as chitosan, pectin, chondroitin sulphate, cyclodextrins, dextran, and guar gum¹¹, have already been tested for their potential as colon-specific drug carrier systems. These natural polymers have a lot of potential as a drug delivery technology that is really colon-specific and commercially available. The reason for this is that they are nontoxic and simple to work with, and the FDA is likely to accept them for medicinal formulations¹². Polysaccharides are employed in dosage forms as prodrugs, matrix systems, and dry coatings by direct tabletting and/or standard coating agents¹³ for colonic delivery. Guar gum is a non-ionic polysaccharide made up of linear chains of (1-4)-β-D-mannopyranosyl units linked by 1-6 links to a-D-galactopyranosyl units. Guar gum is employed as a binder, disintegrant, suspending agent, thickening agent, and stabilising ingredient in pharmaceutical formulations¹⁴. In cold water, guar gum hydrates and swells, generating viscous colloidal dispersions or sols. As a result, it’s employed as a gelling agent to slow down the release of drugs from tablets¹⁵. Due to its biodegradability with colonic enzymes, the potential use of guar gum as a polymer for colon-specific dosage forms has recently been examined. Various medications have been manufactured in matrix or
compression coated tablets containing guar gum for this purpose. Methacrylic acid polymers, such as Eudragit L100, are pH-dependent coating polymers that are utilised to coat solid dosage forms because they solubilize at pH 7. The main goal was to create a single coating layer that would inhibit medication release in the stomach or small intestine while also slowing drug release in the target region (colon)\textsuperscript{16,17}. Mesalamine, the active component of Sulphasalazine, is available in specifically formulated oral and rectal forms for the treatment of mild to moderately active ulcerative colitis, as well as maintenance therapy during disease remissions. Pure mesalamine is rapidly and virtually completely absorbed whether administered directly in the proximal region of the small intestine or orally as a typical tablet, with minimal medication reaching the distal small intestine and colon\textsuperscript{18}. As a result, enteric coated tablets or colonspecific dose forms can be used to prevent early absorption of mesalamine. Orally administered delayed-release mesalamine operates locally in the inflamed intestinal lumen and is partially absorbed into the systemic circulation. Because mesalamine’s efficacy in IBD treatment is related to local action, the site of release and allowing for low systemic absorption, which is meant to limit the incidence of systemic side effects, are the most significant features for its therapeutic application\textsuperscript{19}. Matrix tablets are affordable and straightforward to make with traditional tableting equipment, and their formulation has fewer processing variables. Several model medications have been used to study guar gum in the form of matrix tablets. As a result, the goal of this research was to create a colon-specific matrix tablet of mesalamine including the natural polysaccharide guar gum.

**MATERIALS AND METHODS**

**Materials**

Mesalamine was procured from Dr. Reddy’s Laboratory, Hyderabad, India. Gaur gum was obtained from Central Drug House (CDR), Delhi. Microcrystalline cellulose, starch, talc was purchased from Loba chem Pvt. Ltd., Mumbai (India) and magnesium stearate was purchased from Moly chem Mumbai (India). All other solvents and reagents were purchased from Merck (Germany) and were of analytical grade.

**Methods**

**Preformulation studies**

**Preparation calibration curve of mesalamine**

To make (1000 µg/ml) standard stock solution, 100 mg of medication was carefully weighed and diluted in 100 ml 0.1N HCl (1.2 pH) in a 100 ml volumetric flask (1). Then 10 ml of stock solution (1) was placed in another 100 ml volumetric flask to make (100 µg/ml) standard stock solution (2), then 1,2,3,4,5,6, and 7 ml of stock solution (2) was placed in another 10 ml volumetric flask, and final concentrations of 0.1N HCl (1.2 pH). The absorbance of the standard mixture was measured at 232.55 nm with a UV/VIS spectrophotometer (UV-1700 Shimadzu, Japan). The square of the correlation coefficient (r²), which was derived by least-square linear regression analysis, was used to examine the linearity of the standard curve.

**Drug-excipients compatibility study**

To confirm the compatibility of medicines and excipients, FTIR spectra of pure drugs, polymers employed, and mixes were recorded on KBr disc technique using Brukers Alpha Spectrophotometer with IR solution software. In a glass mortar and pestle, sample powder was completely mixed with potassium bromide before being compacted into discs in a hydraulic press (Techno search Instruments, India). All of the samples’ FTIR spectra were acquired using 20 scans with a resolution of 4 cm\textsuperscript{-1} throughout a spectral range of 4700 to 400 cm\textsuperscript{-1}.

**Pre compression evaluation**

Angle of repose, bulk density, tapped density, Carr’s index, and Hausner’s ratio were used to analyze the flow and compressibility qualities of a powder mixture.

**Angle of repose (θ)**

The fixed funnel method was used to determine the angle of repose. Drug physical mixtures with various excipients were made, and the precisely weighed drug powder or physical combination was placed in a funnel. The height of the funnel was modified such that the tip of the funnel just touches the top of the medication powder heap. The powder was allowed to freely flow out of the funnel onto the surface. The following equation was used to compute the angle of repose.

\[ \theta = \tan^{-1}(h/r) \]

Where, h and r are the height and radius of the powder cone respectively.

**Bulk density**

The following formulas were used to calculate both the loose bulk density (LBD) and the tapped density (TBD).

\[ \text{LBD} = \frac{\text{Powder weight}}{\text{volume of the packing}} \]

\[ \text{TBD} = \frac{\text{Powder weight}}{\text{tapped volume of the packing}} \]

**Compressibility index**

The compressibility index of the granules was determined by Carr’s compressibility index.

\[ \text{Carr's index} \% = \left(\frac{\text{TBD} - \text{LBD}}{\text{TBD}}\right) \times 100. \]

**Hausner’s ratio**

Hausner’s ratio is a measure of how easy it is to measure powder flow. The following formula\textsuperscript{20, 21} was used to calculate it.

\[ \text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}. \]

**Preparation of the matrix tablets**

Direct compression was used to make several tablet batch formulas (F1-F5). In a mortar and pestle, pure medicine (Mesalamine) and polymers (Gaur gum) were put through #40 sieves and combined well for 10 minutes. After passing through #40 sieves, lactose (diluent) was added to this mixture and thoroughly mixed for 5 minutes. After passing through #60 sieves, this powder blend was lubricated with enough magnesium stearate and talc, and then directly compressed into tablets using a single punch rotary tablet machine (Rimek tablet mini press, Ahmadabad) with 10 mm flat punches. Table 1 lists the ingredients in the formulation.
Enteric coating of the matrix tablets

The Eudragit L100 solution was then applied to the mesalamine matrix tablets. In a mixture of ethanol, polyethylene glycol 400 (5 percent w/v), and water, different concentrations of Eudragit L100 coating solution (5 percent, 10 percent, and 20 percent w/v) were created (1:1). The matrix tablets were coated using a dip coating technique after being immersed in the coating solution.

Post-compression parameters

Shape of tablet

The form of the tablet was evaluated under a magnifying lens on directly compressed tablets.

Thickness

Twenty tablets were randomly selected from the representative sample and their thickness was measured using a digital vernier caliper.[22-25]

Hardness

The Monsanto hardness tester was used to determine the hardness of the tablets. Six pills from each batch were tested for hardness, with an average of six results and standard deviations recorded.

Friability test

Ten pills were carefully weighed and placed in the friability test instrument from each batch (Roche friabilator). The apparatus was rotated at 25 rpm for 4 minutes while tablets were observed. After 100 rotations, the tablets were removed, dusted, and reweighed. The percentage weight loss was used to calculate the friability.

\[
\% \text{ Friability} = \left( \frac{W1 - W2}{W1} \right) \times 100
\]

Where \( W1 \) = Initial weight of the 10 tablets, \( W2 \) = Final weight of the 10 tablets after testing.

Friability ratings of less than 0.5-1 percent are usually considered acceptable.

Weight variation test

Weight fluctuation is being investigated. Using an electronic balance, the individual weights (WI) of 20 tablets from each formulation were recorded. It was determined what their average weight (WA) was. The following is how the percent weight variance was computed. The average weights of the tablets were computed, as well as their standard deviations.

Drug content

Five tablets from each formulation were triturated with a mortar and pestle to determine drug content. In a 100 ml volumetric flask, a properly weighed powder equivalent to 250 mg of medicine was diluted with enough phosphate buffer of pH 6.8 to reach the desired concentration. After that, the material was filtered and sonicated for 1 hour. A suitable sample of the filtrate was diluted and spectrophotometrically examined at 331.60 nm against a blank. The test was performed three times and the average drug content was calculated.

Determination of swelling index

The swelling was calculated as a percentage of the tablet's weight gain. All formulations' swelling behaviour was investigated. In a Petri dish containing 6.8 phosphate buffers, one tablet from each formulation was retained. The tablet was removed after 1 hour, soaked in tissue paper, and weighted. The weight of the tablet was then recorded every 2 hours, and the practice was repeated until the entire 16-hour period had passed. The tablet's percent weight gain was determined using a formula:

\[
S.I = \left( \frac{(Mt - Mo)}{Mo} \right) \times 100
\]

Where, \( S.I \) = swelling index, \( Mt \) = weight of the tablet at time \( t \) and \( Mo \) = weight of tablet at time \( t = 0 \).

In-vitro dissolution studies

The USP Type I Apparatus (Paddle type) was used to conduct an in-vitro dissolution study in 0.1 N HCl at 100 rpm for 2 hours (900ml). The dissolution media was then changed with pH 7.4 phosphate buffer (900 ml) and the system was evaluated for 3 hours, as the average small intestine transit time is 3 hours. The dissolution medium was replaced with pH 6.8 phosphate buffer after 5 hours and the results were examined for another 7 hours. Ten milliliters of the sample were taken at the conclusion of the time period and examined for mesalamine concentration. After each sample pullout, a 10 ml fresh and filtered dissolving medium (buffers) was added to make the volume.

RESULTS AND DISCUSSION

Mesalamine was soluble in methanol and ethanol and was freely soluble in water. Mesalamine had a melting point of 280-282°C and a pH of 7.2, respectively. At pH 7.2, the partition coefficient and loss on drying of mesalamine were determined to be 11.7 and 8%, respectively. Using a UV spectrophotometer (UV-1700 Shimadzu, Japan) in the linearity range 10-50g/ml, the maximum of mesalamine was found to be 232.5, 329.5, and 331 nm in 0.1N HCl, phosphate buffers pH 6.8 and pH 7.4 respectively. Fig.1. FTIR spectroscopy was used to identify mesalamine in relation to a marker component. As per the specification, it was recognized from the IR spectrum result. Fig.2. Various pre-compression parameters were applied to the tablet powder blend. Table No. 2 The powder blend’s angle of repose values indicate that it has good flow properties. All of the

| S. No. | Ingredients                  | F1  | F2  | F3  | F4  | F5  |
|-------|------------------------------|-----|-----|-----|-----|-----|
| 1     | Mesalamine                  | 250 | 250 | 250 | 250 | 250 |
| 2     | Gaur Gum                     | 75  | 50  | 37.5| 25  | 12.5|
| 3     | Microcrystalline Cellulose  | 22.5| 47.5| 60  | 73  | 85  |
| 4     | Starch (10%)                 | 25  | 25  | 25  | 25  | 25  |
| 5     | Talc                         | 5   | 5   | 5   | 5   | 5   |
| 6     | Magnesium Stearate           | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| 7     | Total                        | 380 | 380 | 380 | 380 | 380 |

Table 1: Composition of matrix tablet of mesalamine
formulations had bulk densities ranging from 0.3120.005 to 0.3480.016 (gm/ml), indicating that the powder had good flow qualities. All of the formulations’ tapped density was determined to be between 0.5020.007 and 0.5650.005, indicating that the powder has good flow qualities. All of the formulations had compressibility indices ranging from 31.271.27 to 44.600.26, indicating that the powder had good flow qualities. The Hauser’s ratio in all of the formulations ranged from 1.150.02 to 1.200.10, showing that the powder has good flow qualities. All of the formulations from different batches met the required weight uniformity requirements. The matrix tablets had a hardness range of 50.08 to 6.60.21kg/cm2 and a friability of less than 0.7 percent, indicating that they were compact and hard. The tablets’ thickness ranged from 4.020.32mm to 4.350.05mm. All of the formulations met the medication’s content requirements, containing between 2420.18% and 2580.04% mesalamine, with good drug content uniformity. As a result, all of the physical characteristics of the prepared tablets were found to be virtually under control. The tablets were tested for in vitro dissolving for 12 hours in various dissolution solutions (pH 1.2, 6.8, 7.4). The results of the optimised formulation F5 showed that at the end of 12 hours, the drug release was at its maximum, 91.42 percent. Table 4 displays the results of formulation release studies. As a result, F5 was selected and coated with inner and outer coating materials before being evaluated for further research. The weight variation, thickness, hardness, friability, and medication content of tablets of various formulations with coating were exposed to various evaluation tests. The findings of the physicochemical examination of all batches of mesalamine coated matrix tablets are provided in Table 5. In-vitro drug release experiments in various gastric and intestinal fluids revealed that the coated formulations were gastro resistant for 2 hours at pH 1.2 and 3 hours at pH 7.4, releasing less than 10% of the medication (Fig. 3).

Figure 1: UV spectra of curve of mesalamine in 0.1N HCl

Figure 2: IR spectrum of (A) pure drug mesalamine (B) Drug+ Gaur gum
### Table 2: Result of pre-compression properties of mesalamine matrix tablets

| Formulations | Bulk Density (g/ml)* (± SD) | Tapped Density (g/ml)* (± SD) | Compressibility Index (%)* (± SD) | Angle of Repose* (± SD) | Hauser's ratio |
|--------------|-----------------------------|------------------------------|----------------------------------|------------------------|----------------|
| F1           | 0.345±0.025                 | 0.502±0.007                  | 31.27±1.27                       | 20.30±0.22             | 1.18±0.01      |
| F2           | 0.312±0.005                 | 0.562±0.002                  | 44.48±0.20                       | 22.79±0.08             | 1.19±0.01      |
| F3           | 0.348±0.016                 | 0.507±0.009                  | 31.36±0.17                       | 20.80±1.47             | 1.15±0.02      |
| F4           | 0.313±0.020                 | 0.565±0.005                  | 44.60±0.26                       | 24.22±0.46             | 1.20±0.10      |
| F5           | 0.313±0.025                 | 0.513±0.002                  | 38.98±0.02                       | 23.26±0.05             | 1.16±0.02      |

### Table 3: Results of post compression properties of mesalamine matrix tablets

| Formulation | Thickness ± SD*(mm) | Hardness (kg/cm2) ± SD* | Friability ± SD* | Weight Uniformity (mg) ± SD* | Uniformity of content ± SD* | Swelling Index |
|-------------|---------------------|-------------------------|------------------|-----------------------------|-----------------------------|----------------|
| F1          | 4.06±0.025          | 6.6±0.21                | 0.62±0.01        | 0.377±0.45                  | 258±0.04                    | 62.3           |
| F2          | 4.35±0.05           | 5±0.48                  | 0.6±0.25         | 0.378±0.24                  | 242±0.18                    | 59.4           |
| F3          | 4.12±0.12           | 5±0.02                  | 0.64±0.54        | 0.378±0.63                  | 248±0.02                    | 54.2           |
| F4          | 4.02±0.32           | 6±0.25                  | 0.59±0.62        | 0.380±0.17                  | 251±0.033                   | 47.2           |
| F5          | 4.32±0.04           | 5±0.08                  | 0.59±0.88        | 0.378±0.05                  | 249±0.014                   | 41.7           |

All values are mean ± SD, n=3

### Table 4: In-vitro drug release data for formulation F1-F5

| Time (hrs) | % Drug Release |
|------------|----------------|
|            | F1   | F2   | F3   | F4   | F5   |
| 1          | 7.33 | 8.8  | 9.0  | 9.43 | 10.81|
| 2          | 12.46| 11.7 | 16.22| 19.86| 21.53|
| 3          | 16.70| 16.8 | 21.6 | 28.82| 29.62|
| 4          | 21.32| 22.5 | 28.54| 32.41| 34.60|
| 5          | 24   | 26.41| 34.66| 38.55| 40.34|
| 6          | 26.2 | 29.11| 39.70| 45.20| 48.91|
| 7          | 30.2 | 32.8 | 45.90| 49.87| 55.40|
| 8          | 35.42| 36.92| 48.13| 53.61| 62.53|
| 9          | 38.1 | 42.53| 51.93| 58.33| 74.33|
| 10         | 41.55| 46.88| 54.47| 66.28| 82.58|
| 11         | 45.21| 51.64| 59.33| 71.54| 86.22|
| 12         | 46.39| 54.76| 62.11| 75.87| 91.42|

### Table 5: Evaluation of enteric coated tablets of mesalamine

| Parameters                        | E1                | E2                | E3                |
|-----------------------------------|-------------------|-------------------|-------------------|
| Hardness                          | 6.26±0.025        | 6.31±0.06         | 7.54±0.12         |
| Thickness                         | 6.84±0.2          | 7.03±0.008        | 7.12±0.02         |
| Friability                        | 0.58±0.6          | 0.56±1.12         | 0.54±0.44         |
| Weight variation                  | 383±0.32          | 388±0.16          | 812±0.21          |
| Disintegration time (min) (in pH 1.2) | 30                | 40                | Not disintegrated |
| Disintegration time (min) pH 6.8   | 4                 | 7                 | 10                |
Figure 3: in-vitro drug release studies of optimized coated tablet

CONCLUSION

Wet granulation can be replaced with direct compression methods because it is a more straightforward, simplified, and cost-effective method of tablet production. There are several research articles available that show that direct compression is the preferred method of tableting. In vitro drug release experiments have shown that guar gum, in the form of matrix tablets, can prevent the medication from being released in the upper GI tract, i.e. the stomach and small intestine. Mesalamine guar gum matrix tablet formulations could be a promising technique for treating inflammatory bowel disease and other colon diseases. In addition, an in-vivo and pharmacokinetic research must be completed.

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