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Research Article

DEVELOPMENT AND EVALUATION OF MESALAMINE GASTRO-RESISTANT TABLETS

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ABSTRACT

Oral administration is the traditionally preferred route of drug administration providing a convenient method of effectively achieving both local and systemic effects. The colon is believed to be a suitable site where both local and systemic delivery of drugs could be achieved. Colonic drug delivery has gained increased importance not only for localized treatment of several colonic diseases, mainly inflammatory bowel disease (Crohn's disease, ulcerative colitis) and colon cancer. The site specific delivery of drugs (Drug targeting) to lower parts of GIT improve the efficacy of drugs by concentrating the drug molecules at the site of action and minimize systemic side effects and drug instability issues. Consequently, various strategies have been developed for CTDDS (Colon targeted Drug Delivery System), which includes prodrugs, pH and time dependent systems, Bacterial enzyme dependent CDDS, pressure controlled colonic delivery and osmotic controlled drug delivery. Mesalamine is available in a number of oral and rectal (topical) formulations including tablets, micropellets (granules), suppositories and enemas. Several oral formulations have been developed, most of which have been designed with various mechanisms to postpone the release of the release of the active mesalamine compound until reaching the terminal ileum/colon in order to prevent proximal absorption in the small intestine.

The present study involves development and *in-vitro* evaluation of Mesalamine gastro resistant under colon drug delivery system for improving bioavailability by prolonging gastric retention time with the help of pH dependent polymer, which prevent the premature release of mesalamine in the small intestine.

Keywords: Inflammatory bowel disease, Drug targeting, CTDDS, Mesalamine.

1. INTRODUCTION

The major goal of any drug delivery system is to supply a therapeutic amount of drug to a target site in a body, so that the desired drug concentration can be achieved swiftly and then maintained. Colonic delivery refers to targeted delivery of drugs into the lower gastrointestinal tract, which occurs primarily in the large intestine (i.e. colon). Colonic delivery is beneficial for treating the colonic disorder such as inflammatory bowel diseases i.e. ulcerative colitis, Crohn's diseases, Colon cancer and Amoebiasis and also has potential to deliver macromolecular drugs orally. Majority of the research has focused on delivery of drug to the small intestine [1-4]. The large intestine, however, because of its remoteness and relatively different physiology acquired the status of an outcast. From last two decades, interest in area development of oral colon targeted drug delivery systems (CTDDS) has increased, for treatment of local colonic disorders [5].

Mesalamine is an aminosalicylate anti-inflammatory drug used to treat inflammatory bowel disease, including ulcerative colitis (a condition which causes swelling and sores in the lining of the colon [large intestine] and rectum), or inflamed anus or rectum, and to maintain remission in Crohn's disease [6]. It works by stopping the body from producing a certain substance that may cause inflammation. Mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon [7].

The present work aim for the following-

1. As Mesalamine is rapidly absorbed from the small intestine and it is necessary to develop a colon-specific delivery system for it [8].
2. To improve the therapeutic effects of drug (Mesalamine) by concentrating drug molecules at the target site (Colon).
3. To overcome the problem of premature release of drug by addition of functional coating over the core of Mesalamine.

4. To increase the gastric retention or residence time of the drug in the stomach and release their active ingredients in the colon [9].
5. To develop a stable and reproducible drug delivery system of Mesalamine.
6. To minimize the side effects by concentrating the drug on targeted tissues other than non-targeted.

2. MATERIALS AND METHODS

The change in the pH along the gastrointestinal tract has been used as a mean for colon targeted drug delivery. This can be achieved by means of coating that are intact at lower pH of the stomach but that will dissolved at neutral pH of the colon. The pH in the gastrointestinal tract varies from 1.2 in the stomach, 6.6 in the proximal small intestine and about 7.5 in the distal part of small intestine. This pH variation CTDDS in the stomach and small intestine has previously been used to deliver drugs to small intestine by way of pH sensitive enteric coating. These polymer coats are recalcitrant to the acidic condition of the stomach but ionize and get dissolved above a certain threshold alkaline pH found in small intestine. Thus it is possible to apply same concept to deliver drugs to the terminal of ileum or colon by use of enteric polymers with a relatively high threshold pH for dissolution and subsequent drug release.

Current study involved the development of gastro resistant tablets of Mesalamine. The experimental work was divided into preformulation studies, formulation development and characterization of formulations. After the results obtained by preformulation analysis and study on API properties, it was decided to prepare tablets by wet granulation process [10].

In the present investigation, gastro-resistant tablets of mesalamine was formulated by using Microcrystalline cellulose (Diluent), Sodium Starch Glycolate (S.S.G.) (Disintegrant), Polyvinyl Pyrrolidone (P.V.P.K.-30) (Binder), Talcum (Glidant), Colloidal Silicon Dioxide (Glidant) and Magnesium Stearate (Lubricant).

To overcome the problem of premature release of mesalamine, a copolymer of Methacrylic Acid and Methyl Methacrylate Copolymer Type B in different concentrations was used in formulation F1, F2, F3, F4, which dissolve at slower rate and at higher threshold pH 7 to 7.5 and in formulation F5, F6, F7, F8 Acrycoat S-100 was used to prevent the problem of premature release of mesalamine [11].

2.1. Preformulation studies

Preformulation study is the first step in the development of dosage form of drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to get the information for the development of a stable and bioavailable dosage form.

2.1.1. FTIR

The identification of pure drug was done by FTIR spectroscopy technique. FTIR spectroscopy was performed on Fourier transformed infrared spectrophotometer [12]. The pellets of drug and potassium bromide were prepared by compressing the powders at 20 psi for 10 mints on KBr press and the spectra were scanned in the wave number range of 600-4000cm^{-1}.

2.1.2. Melting Point

Melting point of pure drug was checked by capillary method.

2.2. Construction of calibration curve by UV-Visible Spectrophotometer

2.2.1. Calibration curve of Mesalamine in 0.1 N HCl pH 1.2

2.2.1.1. Preparation of stock solution

10 mg of mesalamine was accurately weighed and transformed to 100 ml clean and dry volumetric flask and 70 ml of solution of 0.1 N HCl pH 1.2 and sonicated to dissolve the drug completely and made up the volume with same solvent *i.e,* 0.1 N HCl pH 1.2.

2.2.1.2. Preparation of Sub-stock solution

Sub-stock solutions of mesalamine were prepared by taking aliquot from stock solution and diluted them using 0.1 N HCl pH 1.2. Absorbance was taken at 301.8 nm.

2.2.1.3. Preparation of calibration curve

For the calibration curve of the mesalamine standard stock solution and sub stock solution of mesalamine was prepared in solution of 0.1 N HCl pH 1.2 and plotted the graph between concentration v/s absorbance [13].

2.2.2. Calibration curve of Mesalamine in PBS pH 6.0

2.2.2.1. Preparation of stock solution

10 mg of mesalamine was accurately weighed and transformed to 100 ml clean and dry volumetric flask and 70 ml of solution pH 6.0 phosphate buffer and sonicate to dissolve the drug completely and made up the volume with same solvent pH 6.0 phosphate buffer.

2.2.2.2. Preparation of Sub-stock solution

Sub-stock solution of mesalamine was prepared by taking aliquot from stock solution and diluted them using same solvent pH 6.0 Phosphate buffer. Taken the absorbance at 330.8 nm.

2.2.2.3. Preparation of calibration curve

For the calibration curve of the mesalamine standard stock solution and sub stock solution of mesalamine was prepared in solution of pH 6.0 Phosphate buffer and plot the graph between concentration v/s absorbance.

2.3. Formulation Development

Weighed accurately according to table 2, Sift mesalamine through sieve #24, microcrystalline cellulose through sieve #40 and sodium starch glycolate through sieve #40. Sifted mesalamine, microcrystalline cellulose and sodium starch glycolate were mixed for 10 minutes. Granulation was done using binder solution of PVPK-30 in purified water and wet mass passed through sieve #8 and dry the granules in the tray dryer at temperature between 60-70°C. Sift the dried granules through sieve #20. Sized granules were lubricated with sifted sodium starch glycolate (#40), talcum (#40), colloidal silicon dioxide (#40) and magnesium stearate (#40). Compressed the lubricated the blend using rotary compession machine. Compressed tablets were checked for in-process parameters [13].

2.4. Characterization and Evaluation of Granules and Lubricated Blend

2.4.1. Sieve Analysis

A sieve analysis is a procedure used to assess the particle size distribution of a granular material by allowing the material to pass through a series of sieves of progressively smaller mesh size and weighing the amount of material that is retained on each sieve as a fraction of whole mass [14, 15].

2.4.2. Angle of Repose

The angle of repose is a constant three-dimensional angle assumed by a cone like pile of materials formed. The granules were allowed to fall freely through a funnel fixed at 1 cm above the horizontal flat surface until apex of conical pile just touches the tip of the funnel [16-19].

The angle of repose was determined by the formula-

$$\Theta = \text{Tan}^{-1}h/r$$

Where, h = Height of pile

r = Radius of the pile formed by the granules on the ground.

2.4.3. Bulk Density

Bulk density of granules was determined by pouring gently 20gm of sample through a glass funnel into a 100 ml graduated measuring cylinder. The volume occupied by sample is recorded [20]. Bulk density was calculated as-

$$\text{Bulk Density (g/ml)} = \frac{\text{Weight of sample in grams}}{\text{Volume occupied by sample}}$$

2.4.4. Tapped Density

Tapped Density of granules was determined by pouring gently 20gm of sample through a glass funnel into a 100 ml graduated measuring cylinder. To determine the Tapped Density of granules, the cylinder was tapped from height of 2 inches until a constant volume was obtained [21, 22]. Volume occupied by sample after tapping was recorded and calculated as-

Tapped Density (g/ml) = Weight of sample in grams/ Volume occupied by sample after tapping

2.4.5. Carr's Index

It is also one of the simple methods to measure the flow property of powder by comparing the bulk density and tapped density. The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of materials [23, 24].

$$\text{Carr's Index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \text{X100}$$

2.4.6. Hausner's Ratio

It provides an indication of the degree of densification [25].

$$\text{Hausner's Ratio} = \frac{\text{tapped density}}{\text{bulk density}} \text{X100}$$

2.5. Characterization and Evaluation of Core Tablets

2.5.1. Description

Prepared mesalamine gastro resistant tablets were observed for colour, shape.

2.5.2. Dimensions

Dimensions of tablets were checked by vernier calliper. The tablets held between the jaws of the caliper and slided the adjustable jaws towards the tablet till it held firmly between the jaws.

2.5.3. Average Weight

Taken 20 tablets and weighed accurately on balance. Divided the total weight by 20 and calculated the average weight.

2.5.4. Uniformity of Weight

A tablet designed to contain a specific amount of drug in a specific amount of tablet formula, weight of the tablet being measured to ensure that a tablet contain the proper amount of the drug. USP weight variation test was run by weighing 20 tablets individually and then calculated average weight and compared the individual tablet weights to the average weight [26].

The tablet meets the USP test if not more than 2 tablets are outside the % limit and if no tablet differs by more than 2 times the % limit.

Weighted each tablet individually, as obtained from the average weight test, selected minimum and maximum weight and calculate variation by formula given as (in %)

$$\text{For } (-)\text{ Variation} = \frac{\text{Minimum weight} - \text{Average weight}}{\text{Average weight}} \text{X100}$$

$$\text{For } (+)\text{ Variation} = \frac{\text{Maximum weight} - \text{Average weight}}{\text{Average weight}} \text{X100}$$

2.5.5. Hardness

The resistance of the tablets to chipping, abrasion or breakage under the condition of storage, transportation and handling before usage depends on its hardness. Several devices are used to test tablet hardness such as Monsanto tester, Strong-cobb tester, Pfizer tester [27, 28]. Unit of hardness is Kg/cm^2. The optimum hardness regarded for uncoated tablet is 4-6 Kg/cm^2.

2.5.6. Friability

It's a measure of mechanical strength of tablet using Roche Apparatus. The pre weighed tablets were placed in the friabilator, consist of a plastic chamber that revolves at 25rpm, dropping the tablets at a distance of 6 inches in each revolution. The tablets were rotated in the friabilator for 4 min. [29].

At the end of test, tablets were dusted and reweighed. The loss is weighed and friability is expressed in the terms of percentage as-

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \text{X100}$$

2.5.7. Disintegration Time

For most of the tablets, first important step towards the solution is the breakdown of the tablets in to smaller particle or granules, a process known as disintegration. The USP device used to test disintegration contains 6 glass tubes that are 3 inches long, open at the top and held against a 10 mesh screen at the bottom end of the basket rack assembly.

To test disintegration placed one tablet in each of 6 tubes of the basket rack was positioned in a one liter beaker of water at 37±2°C such that tablet remained 2.5 cm below the surface of the liquid on their upward movement and descend not closer than 2.5 cm from the bottom of the beaker. A standard drive device was used to move the basket assembly containing the tablets up and down through the distance of 5-6 cm at a frequency of 28 to 32 cycles/min [30].

2.6. Characterization and Evaluation of Coated Tablets

2.6.1. Description

Prepared mesalamine gastro resistant tablets were observed for colour, shape.

2.6.2. Dimensions

Dimensions of tablets were checked by vernier calliper. Held the tablets between the jaws of the caliper and slide the adjustable jaw towards the tablet till it is held firmly between the jaws.

2.6.3. Average Weight

Taken 20 tablets and weighed accurately on balance. Divided the total weight by 20 and calculate the average weight.

2.6.4. Uniformity of Drug Content

For determination of drug content, five tablets from each formulation were triturated using mortar and pestle. An accurately weighed powder equivalent to 800 mg of drug was taken in 100 ml volumetric flask and diluted with sufficient amount of phosphate buffer of pH 7.2 up to mark. Then the sample was filtered. An aliquot of the filtrate was diluted suitably and analyzed spectrophotometrically at 330.0 nm. The test was done in triplicate and average drug content was estimated [31].

2.6.5. Dissolution study

The ability of the prepared Mesalamine gastro resistant tablets to retard the drug release in the physiological environment of the stomach and the small intestine was assessed by conducting drug release studies in simulated stomach and small intestine pH, respectively.

2.6.6. Acid Stage I- pH 1.2

Dissolution test was conducted in USP type II apparatus at 100 rpm 37 ±0.5°C for 2 hours in 0.1 N HCl (500 ml) as the average gastric emptying time is about 2 hrs. 5 ml of aliquot fluid was withdrawn, then the remaining solution was discarded and the tablets were retained in the proper order, so that each could be returned to its

respective vessel later on. Blot the tablets with a paper Acceptance criteria- The drug release should be less than 1%.

2.6.7. Buffer Stage I- pH 6.0

The dissolution medium was replaced with pH 6.0 phosphate buffer 900 ml. Tablets were placed in the respective vessels taken from the acid stage with the equilibrated temperature 37 ±0.5°C for 1 hour and tested for drug release for 1 hour with 100 rpm. At the end of time period 5 ml sample was taken and analysed for mesalamine by UV and proceded for Buffer stage II. Acceptance criteria- The drug release should be less than 1% .

2.6.8. Buffer Stage II- pH 7.2

The dissolution medium was replaced with pH 7.2 phosphate buffer 900 ml. Tablets were placed in the respective vessels taken from the buffer stage I with the equilibrated temperature 37 ±0.5°C for 90 minutes at 100 rpm. At the end of time period an aliquot of sample was taken and analysed for mesalamine by UV.

Acceptance criteria- The drug release should not be less than 80% in the phosphate buffer.

3. RESULTS AND DISCUSSION

3.1. Preformulation studies

3.1.1. Fourier transmission Infrared (FT-IR) Spectral analysis

All characteristic peaks of Mesalamine were observed in the IR spectra. No significant shifts are observed in the positions of wave numbers when compared to that of pure drug.

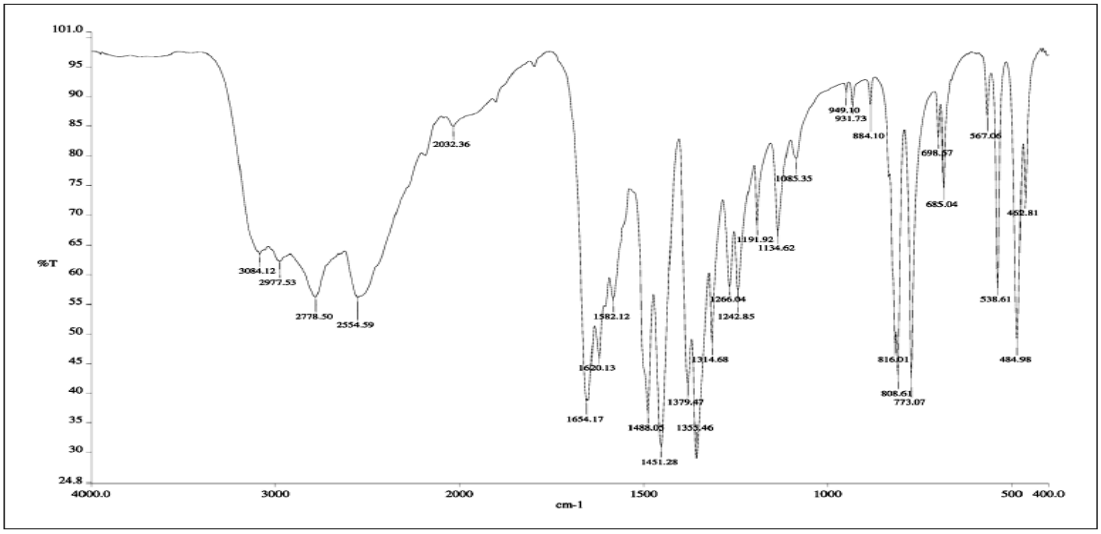

Fig. 1: FTIR spectra of Mesalamine

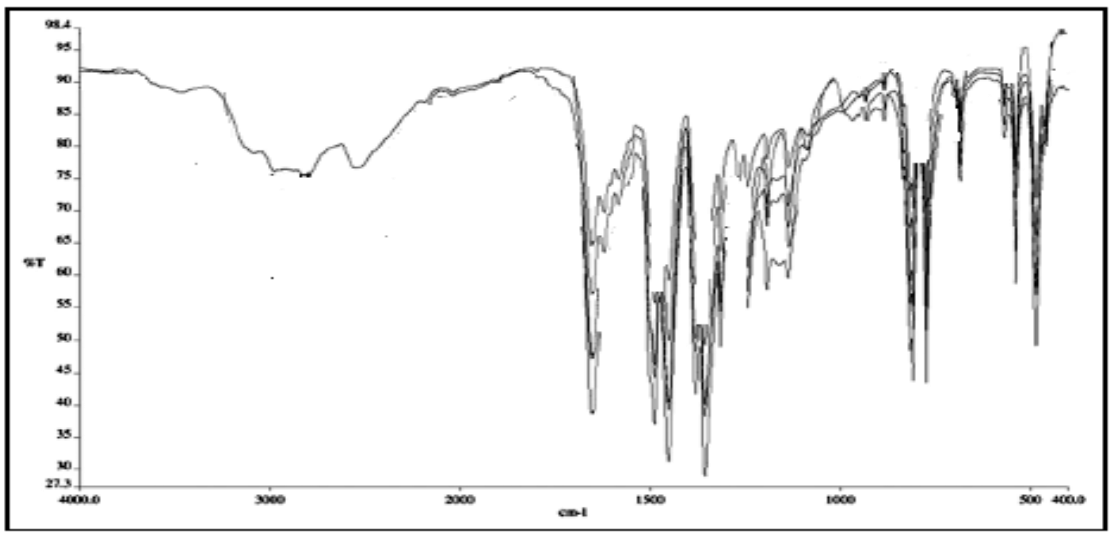

Fig. 2: FTIR spectra of Mesalamine and Methacrylic Acid and Methyl Methacrylate Copolymer Type B

FTIR spectrum of mesalamine showed characteristic peaks at 3084.12 cm^{-1} due to O-H Stretching mode associated with the hydroxyl group, at 2977.53 cm^{-1} due to C-H stretch of the aromatic group, at 1620.13 cm^{-1} due to C = C stretch of the aromatic group; N-H bond scissoring, at 1451.28, 1488.05 cm^{-1} due to C-C stretching mode, at 1355.46, 1379.47 cm^{-1} due to O-H deformation of the hydroxyl groups, at 1134.62 cm^{-1} due to C-O stretching mode.

FTIR spectrum of Eudragit S-100 showed characteristic peaks at 2953.9 cm^{-1} due to presence of O-H (carboxylic acid), at 1450.7 cm^{-1} due to $-CH_3$ bend and at 1731.5 cm-1 due to presence of C=O (ester). Therefore, FTIR study concluded that no interaction occurred between the drug and polymer.

3.1.2. Melting Point

The melting point of Mesalamine was determined using melting point apparatus. The sample was placed in capillary which was placed in apparatus and the temperature at which the sample is starting to melt at 282°C.

3.1.3. Solubility of Drug

The drug Mesalamine is slightly soluble in water, alcohol, more soluble in hot water, soluble in HCl, insoluble in ethanol.

3.1.4. Particle size analysis

D10 diameter is the diameter at which 10% of sample mass is comprised of 5.766 µm particles, and D50 diameter is the diameter at which 50% of sample mass is comprised of 18.573 µm particles and D90 diameter is the diameter at which 90% of sample mass is comprised of 70.532 µm particles.

Table 1: Particle size Analysis

Drug Substance	D (0.10)	D (0.50)	D (0.90)
Mesalamine	5.766 µm	18.573 µm	70.532 µm

3.2. Characterization and Evaluation of Granules and Lubricated Blend

The granules of mesalamine gastro resistant tablets were prepared by wet granulation method according to table 18 and 20. The granules were characterized with respect to angle of repose, Bulk density, tapped density, carr's index ang Hausner's ratio. The parameters for evaluation of granules are depicted in table 5, 6 and 7. The angle of repose of different formulation batches from F1-F8 was found to be from 29.0° to 38.6°. The angle of repose was less than 30° for all the formulation batches of granules, indicating good flow behavior.

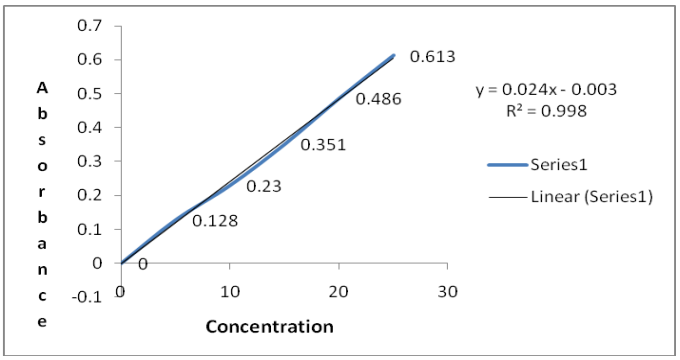

Fig. 3: Calibration curve of Mesalamine in 0.1 N HCl pH 1.2

Table 2: Composition of Core Tablets of Mesalamine (F1, F2, F3, F4, F5, F6, F7, F8)

S. N.	Ingredients	Mg/tab	Mg/tab	Mg/tab	Mg/tab	Mg/tab	Mg/tab	Mg/tab	Mg/tab
	Formulations	**F1**	**F2**	**F3**	**F4***	**F5**	**F6**	**F7**	**F8**
Premix Materials									
1.	Mesalamine	800	800	800	800	800	800	800	800
2.	Microcrystalline Cellulose	49	46	38	41	47.5	61.2	56	57.5
3.	S.S.G.	34	28	25	30	4.5	7	6	5.5
Binder Materials									
4.	P.V.P.K.-30	35	38	45	42	50	30	50	45
5.	Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Lubricants									
6.	S.S.G.	22	25	28	25	31	36	23	30
7.	Talcum	10	10	10	10	9	8	9	6
8.	Colloidal Silicon Dioxide	4	5	6	6	10	10	8	8
9.	Magnesium Stearate	6	8	8	6	8	7.8	8	8
TOTAL		960	960	960	960	960	960	960	960

Table 3: Composition of Coating Materials for Core Tablets of Mesalamine

S. N.	Ingredients	Mg/tab	Mg/tab	Mg/tab	Mg/tab	Mg/tab	Mg/tab	Mg/tab	Mg/tab
	Formulations	F1	F2	F3	F4*	F5	F6	F7	F8
Coating Materials									
PART A									
1.	Methacrylic Acid and Methyl Methacrylate Copolymer Type B	60	65	75	85.50	-----	-----	-----	-----
2.	Acrycoat S-100	-----	-----	-----	-----	95.5	110.8	82	72
3.	Triethyl Citrate	13.60	13.60	13.60	13.60	20.4	20.4	20.4	20.4
4.	Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
5.	Isopropyl Alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
PART B									
6.	Talcum	32.5	32.5	32.5	32.5	48.75	48.75	48.75	48.75
7.	Iron Oxide of Red	2.95	2.95	2.95	2.95	-----	-----	-----	-----
8.	Iron Oxide of Yellow	-----	-----	-----	-----	4.43	4.43	4.43	4.43
9.	Titanium Dioxide	8.86	8.86	8.86	8.86	13.29	13.29	13.29	13.29
10.	Polyethylene Glycol (P.E.G.)-6000	4.43	4.43	4.43	4.43	6.64	6.64	6.64	6.64
11.	Isopropyl Alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
12.	Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
13.	Acetone	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Table 4: Sieve analysis of dried granules

Formulation Code	Sieve number/Sample retained on sieve (gm) or [% Cumulative retention]						
	20 # (840µm	30 # (600µm)	40 # (425µm)	60 # (250µm)	80 # (180µm)	100 # (150µm)	Base
F1	0	7.5 (37.5%)	4.2 (21%)	3.5 (17.5%)	3 (15%)	1 (5%)	0.8 (4%)
F2	0	6.9 (35%)	3.7 (19%)	2.6 (13%)	5 (25%)	0.5 (2.5%)	1.3 (6.5%)
F3	0	4.8 (24%)	8 (40%)	5.2 (26%)	1 (5%)	0.8 (4%)	0.2 (1%)
F4	**0**	**10.3 (52%)**	**4 (20%)**	**2.8 (14%)**	**2 (10%)**	**0.5 (2.5%)**	**0.4 (2%)**
F5	0	8 (40%)	4 (20%)	3.5 (17.5%)	2.8 (14%)	1 (5%)	0.7 (3.5%)
F6	0	6.9 (35%)	4 (20%)	3.9 (20%)	2.7 (14%)	1 (5%)	1.5 (7.5%)
F7	0	9.4 (47%)	3 (15%)	2.8 (14%)	3.3 (17%)	1 (5%)	0.5 (2.5%)
F8	0	9.66 (48%)	4.9 (25%)	1.6 (8%)	2 (10%)	0.74 (3.7%)	1.1 (5.5%)

Table 5: Characteristics of Lubricated Blend

Formulation	Angle of Repose (Θ)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	38.2	0.366	0.447	18.12	1.221
F2	37.5	0.361	0.439	17.77	1.216
F3	38.6	0.366	0.452	19.03	1.235
F4	29.0	0.367	0.409	10.27	1.114
F5	32.9	0.362	0.414	12.56	1.144
F6	33.4	0.365	0.420	13.10	1.151
F7	34.6	0.367	0.417	11.99	1.136
F8	37.4	0.364	0.441	17.46	1.212

Similarly, bulk density and tapped density of all formulation batches from F1-F8 were found to be from 0.361 to 0.367 gm/ml and from 0.414 to 0.452 gm/ml, depicting good flow properties of granules.

The carr's index of all formulations batches was in the acceptable range from 10.27 to 19.03.

The Hausner's ratio of all formulations batches from F1-F8 was found to be from 1.114 to 1.235. The hausner ratio less than 1.25 indicates good flowability.

The formulation F4 had good percentage of granules when compared to other formulations. Hence, lead to good flow property. Sieve analysis results showed average granular size of Mesalamine Blend. After the analysis of Bulk density, tapped density, Carr's index and angle of repose, it was found that the formulation F4 had good percentage of granules when compared to other formulations. Hence, lead to good flow property.

3.3. Characterization and Evaluation of Core Tablets

To develop core tablet batches were prepared by using different concentration of disintegrant (Sodium starch glycolate), binder (PVPK-30), Lubricant (talcum and magnesium stearate) and glidant (colloidal silicon dioxide). And weight of tablet was compensated with diluent (microcrystalline cellulose).

Table 6: Evaluation Parameters of Core Tablets

Formulation Code	Thickness (mm)	Average Weight (mg)	Hardness (kg/cm^2)	Friability (%)	Disintegration Time (minutes)
F1	6.90 ± 0.3	960.8 ± 5 %	5.8 ± 0.15	0.17	9 minutes 20 seconds
F2	7.10 ± 0.3	960.2 ± 5 %	5.74 ± 0.37	0.15	7 minutes 35 seconds
F3	7.00 ± 0.3	960 ± 5 %	6.08 ± 0.13	0.21	8 minutes 47 seconds
F4	7.00 ± 0.3	961.1 ± 5 %	5.1 ± 0.29	0.12	6 minutes 54 seconds
F5	7.30 ± 0.3	960.3 ± 5 %	5.36 ± 0.15	0.20	11 minutes 24 seconds
F6	7.10 ± 0.3	960.4 ± 5 %	5.62 ± 0.11	0.17	9 minutes 51 seconds
F7	6.90 ± 0.3	961.6 ± 5 %	5.27 ± 0.24	0.14	9 minutes 39 seconds
F8	7.00 ± 0.3	960.9 ± 5 %	5.23 ± 0.19	0.16	10 minutes 44 seconds

The uncoated tablets of different formulations were subjected to various evaluation tests of weight variation, thickness, hardness, friability. Post compression parameters like hardness and friability values showed that tablets were mechanically stable. The shapes of tablets in all formulation were found to be elongated and thickness was uniform depending on their individual weight.

The average weight of all formulation batches from F1-F8 was found to be from 960 to 961.6 mg. The weight variation of all batches was less than 5 % which was in acceptable range.

The thickness of all formulations was found to be between 6.90 to 7.30 mm. The hardness of the formulation F1-F4 was found to from 5.1 ± 0.29 to 6.08 ± 0.13 (kg/cm2) and F5-F8 was found to from 5.23 ± 0.19 to 5.62 ± 0.11 (kg/cm^2).

The friability of all tablets in formulation was in acceptable range of less than 1 % ranging from 0.12 to 0.21% w/w.

The percentage weight variation and disintegration time of all the formulations were found to be within pharmacopoeial limits from 6 minutes 54 seconds to 11 minutes 24 seconds.

3.4. Characterization and evaluation of coated tablets

To overcome the problem of premature release of mesalamine, a copolymer of Methacrylic Acid and Methyl Methacrylate Copolymer Type B is used in different concentration in formulation F1, F2, F3, F4, which dissolve at slower rate and at higher threshold pH 7 to 7.5 and in formulation F5, F6, F7, F8 acrycoat S-100 was used in different concentration to prevent the problem of premature release of mesalamine.

Table 7: Evaluation Parameters of Coated Tablets

Formulation Code	Length (mm)	Width (mm)	Thickness (mm)	Average Weight (mg)	Content Uniformity
F1	19.00 ± 0.2	8.90 ± 0.2	7.10 ± 0.4	1044 ± 5 %	99.97 ± 0.55
F2	19.00 ± 0.2	8.90 ± 0.2	7.10 ± 0.4	1046 ± 5 %	100.15 ± 0.56
F3	19.10 ± 0.2	9.00 ± 0.2	7.10 ± 0.4	1062 ± 5 %	100.18 ± 0.74
F4	19.10 ± 0.2	9.00 ± 0.2	7.20 ± 0.4	1087 ± 5 %	101.04 ± 0.68
F5	19.00 ± 0.2	9.00 ± 0.2	7.10 ± 0.4	1061 ± 5 %	99.02 ± 0.95
F6	19.10 ± 0.2	9.00 ± 0.2	7.20 ± 0.4	1079 ± 5 %	99.57 ± 0.31
F7	19.00 ± 0.2	9.00 ± 0.2	7.10 ± 0.4	1063 ± 5 %	95.25 ± 0.25
F8	19.0 0.2	8.90±0.2	7.10± 0.4	1058 ± 5 %	96.75 ± 0.95

Four formulations viz. F1, F2, F3, F4 were coated with Methacrylic Acid and Methyl Methacrylate Copolymer Type B, in which it was used in different concentrations viz. 6.25 %, 6.77 %, 7.86 % and 8.91% respectively, was given 9 %, 9 %, 11 % and 13 % w/w gastro retentive coat to the weight of the tablet respectively.

Another four formulations viz. F5, F6, F7, F8 were coated with Acrycoat S-100, in which it was used in different concentrations viz. 9.95 %, 11.54 %, 8.54 % and 7.5% respectively, was given 11 %, 12 %, 11 % and 10 % w/w gastro retentive coat to the weight of the tablet respectively.

The thickness and average weight of all formulation increased due to coating over the surface of the tablets.

Drug release from all formulations in Acid stage I- pH 1.2 were found to be less than 1% and in Buffer stage I- pH 6.0 were also found to be less than 1%, while in Buffer Stage II- pH 7.2 (Acceptance criteria- The drug release should not be less than 80% in the phosphate buffer) it was found to be different for all formulations viz. 60.98 %, 88.89 %, 92.88 %, 99.97 %, 93.09 %, 94.70 %, 60.90 %, 57.77 % for F1, F2, F3, F4, F5, F6, F7, F8 respectively.

Drug release kinetic parameters are performed like zero-order kinetic model, zero-order kinetic model gave the highest value of the coefficient of determination (R^2) for optimized formulation F4 (0.9974), indicating that zero-order kinetic model would be most suitable model for describing the release of mesalamine shown in Fig.4 and Fig5.

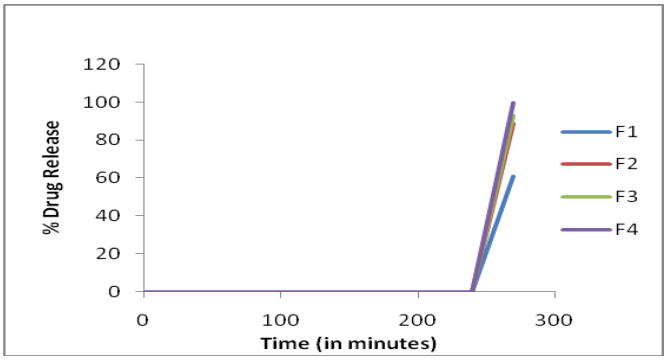

Fig. 4: Comparison of % Drug Release of Formulation F1, F2, F3, F4

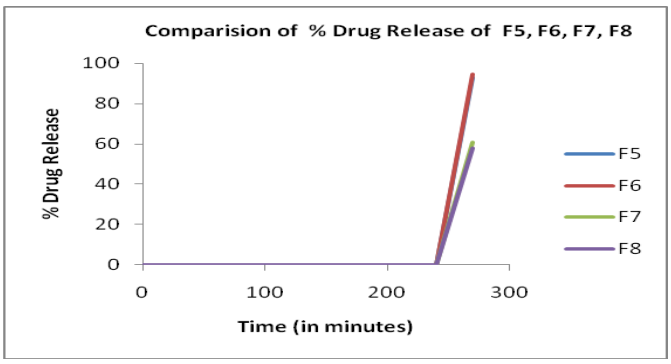

Fig. 5: Comparison of % Drug Release of Formulation F5, F6, F7, F8

Formulation F1, F7 and F8 were not found to be in acceptance limits. On the basis of percentage drug release and content uniformity, the optimum formulation was found to be F4 (coated with Methacrylic Acid and Methyl Methacrylate Copolymer Type B).

It is concluded from the present study that appropriate pH dependent polymer was suitable to protect mesalamine from being released in the upper region of the GI system.

4. CONCLUSION

This report summarizes the development and evaluation of Mesalamine gastro resistant tablets. Development of Mesalamine gastro resistant tablets based on preformulation studies, excipients compatibility studies, optimization studies for consistent delivery and intended performance of the drug product. Mesalamine, also known as mesalazine or 5-aminosalicylic acid (5-ASA), is a medication used to treat inflammatory bowel disease, including ulcerative colitis and crohn's disease. It is generally used for mildly to moderately severe inflammatory bowel disease. It is taken by mouth or rectally. Excipients compatibility is an important part of understanding the role of inactive ingredients in product quality. The selection of excipients for the compatibility study should be based on the mechanistic understanding of the drug substance and its impurities, excipients and their impurities, degradation pathway and potential processing conditions for the drug product manufacturing. A scientifically sound approach should be used in constructing the compatibility studies. The physical and chemical compatibility of drug substance with excipients were carried out with an aim to select suitable excipients for a stable and robust formulation. A blend of drug with excipient in ration as per the formulation was filled in glass vials and charged at temperature 40°C ± 2°C and RH 75 ± 5% and 25°C ± 2°C and RH 60 ± 5% for 28 days. All excipients were selected on the basis of compatibility studies with the excipients. Mesalamine is a BCS class II compound, so particle size of mesalamine plays an important role in the development of the formulation. After the analysis of Bulk density, tapped density, carr's index and angle of repose, it was decided to prepare tablets by wet granulation method. To overcome the problem of premature release of mesalamine, a copolymer of Methacrylic Acid and Methyl Methacrylate Copolymer Type B and acrycoat S-100 are used in different concentration, which dissolve at slower rate and at higher threshold pH 7 to 7.5, to prevent the problem of premature release of mesalamine.

As such initial efforts focused on developing a dissolution method that would be able to predict in-vitro performance. The developed method uses 500 ml of 0.1 N hydrochloric acid for 2 hours at 100 rpm in USP apparatus II (Paddle), Buffer stage I- 900 ml of phosphate buffer pH 6.8 for 1 hour at 100 rpm in USP apparatus II (Paddle), Buffer stage II- 900 ml of phosphate buffer pH 7.4 for 1 hour at 100 rpm in USP apparatus II (Paddle).

5. REFERENCES

1. Singh A, Sharma A, Pooja, Anju. *International journal of Research and Development in Pharmacy and Life Sciences,* 2014; **2(3)**:877-886.
2. Gupta V, Gnanarajan G, Kothiyal P. *The pharma Innovation*, 2012; **7(1)**:14-23.
3. Prathap M, Gulshan M, Rao R. *International Journal of Research in Pharmaceutical and Nano Sciences,* 2014; **3(5)**: 429-437.
4. Brahamankar BM, Jaiswal SB. *Biopharmaceutics and pharmacokinetics to controlled release medication of oral site specific / colon DDS*, 1995;457.
5. Ratnaparkhi M, Somvanshi F, Pawar S, Chaudhari S et al. *International Journal of Pharma Research and Review*, 2013; **2(8):**33-42.
6. Priyanka, Kumar K, Teotia D. *Journal of Drug Delivery and Therapeutics*, 2018; **8(6):**382-390.
7. Raymond C, Paul J et al., *Handbook of Pharmaceutical Excipients, Published by the Pharmaceutical Press and the American Pharmacists Association*, 2009; 6.
8. British national formulary: *BNF 76* Pharmaceutical Press. 2018; **(76)**, 39-41.
9. Bendas E, Christensen J, Ayres J. *Drug Dev Ind Pharm,* 2010; **36(4)**:393-404.
10. Abdulmajed A, Ali A, *Universal Journal of Pharmaceutical Research,* 2018; **3(4)**:42-47.
11. Kumar R, Patil M, Sachin A. *International Journal of Pharm Tech Research,* 2009; **(1)**:334-346.
12. Ali A, Abdulmajed A. *Universal Journal of Pharmaceutical Research,* 2018; **3(4)**:31-36.
13. Ankita P, Dhruvita P, Trupti S, Bharadia P et al. *IJPI's Journal of Pharmaceutics and Cosmetology,* 2011; **1(5):**86-97.
14. Swapnil L, Asish D. *World Journal of Pharmacy and Pharmaceutical Sciences*, 2016; **7(5)**:1235-1266.
15. Satbir S, Tarun V, Reshu V, Pankaj K et al. *Universal Journal of Pharmaceutical Research,* 2018; **3(4)**:60-69.
16. Purushothaman M, Kalvimoorthi V. *International Journal of ChemTech Research*, 2017; **10(10):**156-168.

17. Sharma A, Jain K. *Journal of Pharmaceutical Studies and Research.* 2010; **1(1)**:60-66.
18. Chauhan V, Kumar K, Teotia D. *Universal Journal of Pharmaceutical Research***,** 2017; **2(4):**58-64.
19. Markovic M, Dahan A, Keinan S, Kurnikov I et al. *Pharmaceutics,* 2019; **(11**):186.
20. Oyeniran T, Opeyemi, Obanewa opeyemi Adegbenro. *Universal Journal of Pharmaceutical Research***,** 2018; **3(5)**:68-73.
21. Halsas M, Penttinen T, Veski P, Jurjenson H et al. *Pharmazie* 2001; (**56)**:718-723.
22. Dingwoke J, Felix S. *Universal Journal of Pharmaceutical Research*, 2019; **4(1)**:24-28.
23. Aditya T, Mithun B, Jagdish R. *Journal of Drug Delivery and Therapeutics,* 2018; **8(2):**8-14.
24. Saddam C, Dnyaneshwar S, Dipak V, Shirish J et al. *Universal Journal of Pharmaceutical Research,* 2018; **3(4)**:20-25.
25. Mundhe V, Dodiya S. *Indo American Journal of Pharmaceutical Research,* 2011; **(3)**:158-173.
26. Igwe J Chibueze, Emenike IV, Oduola A. *Universal Journal of Pharmaceutical Research,* 2016; **1(2)**:25-31.
27. Agarwal P, Semimul AA, *Universal Journal of Pharmaceutical Research,* 2018; **3(6):**53-58.
28. Koteshwara KB. *Int. Journal of Research in Ayurvedic and Pharmacy,* 2011; **2 (1)**:60-65.
29. Nweje-A, Anyalogbu E, White A. *Universal Journal of Pharmaceutical Research,* 2017; **2(5)**:18-22.
30. Shah M, Azmat A, Hina A, Khalid N. *Universal Journal of Pharmaceutical Research***,** 2017; **2(6)**:50-52.
31. Bhushan P et al. *Asian Journal of Biomedical and Pharmaceutical Sciences,* 2012; **2(14):**21-28.