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# *MODULATION OF MESALAMINE RELEASE FROM ENTERIC-COATED MATRIX TABLETS USING NATURAL POLYSACCHARIDES FOR LOCALIZED COLONIC DELIVERY*

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***ABSTRACT***
**Background:** Inflammatory Bowel Diseases (IBD) affect the gastrointestinal tract. Delivering drugs directly to the colon enhances therapeutic efficacy and minimizes systemic side effects for IBD treatment. **Objectives:** To develop and evaluate colon-targeted mesalamine matrix tablets for IBD treatment. **Materials and Methods:** Mesalamine matrix tablets were prepared by wet-granulation method consisting of pH-sensitive polymer (HPMC K4M) and natural polysaccharides (pectin, chitosan, guar gum). Tablets were characterized and optimized formulations were enteric-coated. **Results:** The uncoated formulations developed by using 1:1:1 ratios of mesalamine: pectin/chitosan: HPMC K4M (coded as M3 and M6) and 1:1:0.5 ratios of mesalamine: guar gum: HPMC K4M (coded as M7) showed adequate protection against drug release in simulated gastric (0-2 h) and intestinal (2-5 h) fluids. The optimized enteric-coated formulations consisting of pectin, chitosan, and guar gum (coded as ME3, ME6, and ME7, respectively) exhibited a lag time of around 2 hours and restricted drug release of around 4.46%, 5.12 %, and 5.18%, respectively, in simulated gastric and intestinal fluids up to 5 hours. However, in simulated colonic fluid (pH 6.8) containing 4% rat cecal contents, these formulations showed enhanced drug release (71-83% in 12 h) due to biodegradation of polymeric matrices by colonic enzymes. Drug release kinetics indicated anomalous transport or super case-II transport mechanisms. Accelerated Stability studies carried out at 40°C±2°C and 75%±5% for 3 months revealed no significant changes. **Conclusion:** The colon-targeted mesalamine matrix tablets demonstrated potential for colonic delivery, improving therapeutic efficacy and minimizing systemic side effects in IBD treatment.

## *INTRODUCTION*

In recent times, drug delivery systems designed to target the colon have garnered huge interest due to their potential effectiveness in treating localized diseases affecting the colon, along with inflammatory bowel disease (IBD), which refers to

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chronic inflammatory conditions of the gastrointestinal tract, primarily including Crohn's disease and ulcerative colitis. These conditions can significantly impact individuals, healthcare systems, and economies worldwide. According to the latest global estimates, the prevalence of IBD is on the rise, particularly in developed countries and regions undergoing rapid industrialization and urbanization. The global prevalence of Crohn's disease and Ulcerative colitis is estimated to be around 284 and 298 cases per 100,000 individuals, respectively. IBD's prevalence and economic burden can vary across regions and countries and are influenced by factors such as healthcare access, diagnostic practices, and socioeconomic conditions. In the United States alone, the estimated direct healthcare costs for IBD range from $11.6 billion to $16.7 billion annually. In Europe, estimated costs associated with IBD range from €4.2 billion to €6.4 billion annually [1]. The colon presents a striking site for the delivery of proteins, therapeutic peptides, and other drugs susceptible to degradation in the upper part of the gastrointestinal tract (GIT). By precisely targeting drug release to the colon, it becomes possible to decrease the drug's exposure to the hostile environment of the stomach and small intestine, consequently lowering potential side effects and improving the therapeutic efficacy of the administered drug [2]. A drug extensively researched for targeted delivery to the colon is mesalamine (5-aminosalicylic acid), an agent that acts locally and is employed within the remedy of ulcerative colitis and Crohn's disease. The conventional oral formulations of mesalamine often result in significant drug absorption from the upper GIT, leading to decreased drug bioavailability at the preferred site of action and amplified systemic side effects [3]. Various colon-targeted delivery systems of mesalamine developed, like delayed release oral formulations, oral prodrugs (e.g., Balsalazide, Olsalazine), rectal formulations, etc. These existing formulations still face challenges related to variability in gastrointestinal conditions, potential systemic absorption, local side effects, and limitations in site specificity or release profiles. The present research focuses on developing novel colon-targeted matrix tablet formulations of mesalamine, which can be used to overcome the limitations of existing formulation approaches. The matrix tablets were designed to shield the drug to liberate in the upper GIT and facilitate targeted drug release in the colon through the action of colonic enzymes produced by the resident microflora. Diverse formulation techniques, such as wet granulation, enteric coating, and various polymer combinations, were explored to optimize the overall performance of the colon-targeted delivery system [4, 5].

The successful development of such a delivery system could potentially improve the therapeutic efficacy and patient compliance in treating IBDs and other colon-associated diseases [6]. This research investigation aims to develop and evaluate novel colon-targeted mesalamine matrix tablets using a combination of pH-sensitive polymers and natural polysaccharides [7]. This tablet may act as a robust system capable of effectively delivering mesalamine to the targeted site of action in the colon by modulating its release for improved therapeutic efficacy in IBD.

## *MATERIALS AND METHODS*

### Materials

Mesalamine was obtained as a Gift sample from Sun Pharma, Sikkim, India. Eudragit®S100 and Chitosan were received as a Gift sample from Rohm Pharma, India, and Aurobindo Pharma Pvt. Ltd., Chennai, India, respectively. Pectin, Guar gum, Polyvinyl pyrrolidone (PVP), Ethyl Cellulose, and Aerosil were purchased from Lobachemie, Mumbai. HPMC K4M and Lactose were purchased from Colorcon, Mumbai, India, and Finar Chemicals Ltd., Ahmadabad, India.

### Experimental Method

### Characterization of drug and analytical studies

The drug was characterized for Physical appearance, UV spectral analysis, IR Spectral analysis, and DSC.

### Drug polymer compatibility studies

Drug and polymer(s) compatibility studies were carried out by both FTIR and DSC method

**1. By FTIR analysis [8]**

The drug-excipient compatibility analysis used diffuse reflectance Fourier transform infrared (FTIR) spectroscopy. The drug and excipients were mixed in a 1:1 ratio, thoroughly combined, and stored at 40°C with 75% relative humidity and at room temperature for one month. The samples were then mounted in the IR compartment and scanned between the wave number range of 4000 cm-1 to 400 cm-1 using an FTIR spectrophotometer (Spectrum RX1, Model no.-Shimdzu-840-os, Japan). Before sample scanning, a blank air background spectrum was acquired. Pure drug, pure polymers, and their

physical mixtures were scanned, and the resulting FTIR spectra were reported and presented.

**2. Differential Scanning Calorimetric (DSC) analysis [9]**

DSC provides information about the physical properties of the drugs and demonstrates a possible interaction between the drug and other compounds in formulations. Thermal analysis using DSC was carried out on drug(s), a physical mixture of drugs with different polymers and different formulations, using a DSC-6100 (Seiko Instrument, Japan) thermal analyzer. The samples were stored at 40ºC/75% RH for 3 months. After completion of 3 months, 2 mg of samples were loaded into aluminum pans and sealed. The thermal analysis involved subjecting all the samples to a controlled temperature ramp of 20ºC/minute, spanning the temperature range from 40-430°C.

**Formulation and development of Mesalamine Matrix tablets**

Matrix tablets (400 mg) containing 100 mg of Mesalamine were prepared via wet granulation technique [10] using pectin, chitosan, guar gum, and HPMC K4M as matrix formers in varying ratios (Table 1).

These natural polymers have got specific degradability by colonic bacteria, whereas guar gum and HPMC K4M also have potential gelling behavior and rate retarding action. Hence, these polymers are suitable for colon-targeted delivery of mesalamine. In the formulation, lactose served as the diluent. The ingredients were blended, granulated with 5% PVP K-30 in isopropyl alcohol, passed through a #18 mesh sieve, and dried at 50°C for 15-20 minutes. The dried granules were sieved through #22 mesh, lubricated with aerosil and magnesium stearate, and compressed into 13 mm slightly concave round tablets using a multi-punch machine (Rimek, Karnavati Engineering Pvt., Ahmadabad, India) at 20 KN compression force. All formulations (M1-M9) were evaluated for drug content, weight variation, hardness, friability, thickness, and in vitro drug release [11].

**Table 1: Composition formula for Mesalamine matrix tablet**

| Sl. No. | Ingredients (mg) | Formulation codes | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 |
| 1 | Mesalamine | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| 2 | Pectin | 100 | 100 | 100 | - | - | - | - | - | - |
| 3 | Chitosan | - | - | - | 100 | 100 | 100 | - | - | - |
| 4 | Guar gum | - | - | - | - | - | - | 100 | 100 | 100 |
| 5 | HPMC K4M | 50 | 75 | 100 | 50 | 75 | 100 | 50 | 75 | 100 |
| 6 | PVP K-30 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| 7 | Lactose | 125 | 100 | 75 | 125 | 100 | 75 | 125 | 100 | 75 |
| 8 | Aerosil | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 9 | Mg. Stearate | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| | Total weight (mg) | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 |

**Preparation of enteric-coated Mesalamine matrix tablets**

The matrix tablets were coated with an enteric outer layer using a modified dip coating method. A 5% w/v Eudragit® S100 solution in acetone, containing 20% w/w castor oil as a plasticizer, 0.05% w/w titanium dioxide as an opacifier, and 5% w/w talc as anti-adherent, was used for coating [12, 13]. Similarly, a 5% w/v ethyl cellulose solution in acetone was also prepared. The Mesalamine matrix tablets (M1 to M9) were enteric coated with the 5% Eudragit® S100 solution (coded as ME1 to ME9) and the 5% ethyl cellulose solution (coded as MC1 to MC9).

**Table 2: Composition formula for 5% w/v Eudragit® S100 and 5% w/v ethyl cellulose enteric coating solution**

| Ingredients | Strengths in solution | Uses |
|---|---|---|
| Eudragit®S100/ Ethyl Cellulose | 5% w/v of solvent | Coating agent |
| Castor Oil | 20% w/w of polymer | Plasticizer |
| Titanium dioxide | 0.05% w/w of polymer | Opacifier |
| Talc | 5% w/w of polymer | Anti adherent |

***EVALUATION OF COLON-SPECIFIC MESALAMINE TABLET FORMULATIONS***

**Physical characterization of tablets**

Flow characteristics or granular properties characterized the powder blends used to prepare tablets. All batches of tablet formulations were characterized for official evaluation parameters like weight variation, hardness, brittleness, and tablet thickness and reported for further optimization and evaluation.

**Determination of Drug release Lag time**

Lag time was determined for colon-specific tablet formulations. It is the time required for the drug to be released into the dissolution media from the tablet formulations or the period up to which drug release is prevented [14].

**Drug content uniformity**

To perform a content uniformity test, from each batch, ten tablets were finely crushed, and an amount corresponding to 100 mg of mesalamine was exactly weighed and shifted to a 100 mL volumetric flask containing phosphate buffer solution maintained at pH 6.8. The solution was thoroughly mixed, made up to volume, and filtered. The filtrate was diluted suitably, and the absorbance was measured at 330 nm using a Shimadzu UV/Vis double-beam spectrophotometer [15]. The Mesalamine content in the tablet formulations was estimated using the linearity equation obtained from the previously described calibration curve.

***In vitro* drug release study**

*In vitro* drug release study for the formulations performed in the presence and absence of rat cecal contents to evaluate the drug release pattern and rate by using the USP dissolution test procedure.

**(A) *In vitro* drug release from Mesalamine tablet formulations in standard dissolution media**

The in vitro drug release assessment employed a United States Pharmacopeia (USP) compliant basket-type dissolution apparatus (Lab India Tablet Dissolution apparatus, Mumbai, India). The operational parameters included a rotational speed of 100 rpm, a temperature of 37±0.5°C, and a dissolution medium volume of 900 ml. A buffer change technique was implemented to simulate the varying pH conditions encountered in the gastrointestinal tract. The tablets containing Mesalamine were initially suspended in a simulated gastric fluid (SGF) at pH 1.2 for 2 hours. Consequently, the dissolution medium was replaced with a mixture of SGF and simulated intestinal fluid (SIF) at pH 4.5 for 1 hour, followed by 2-hour incubation in SIF at pH 7.4. The release study was extended by introducing simulated colonic fluid at pH 6.8. Throughout the study, sink conditions were maintained to ensure adequate solubility and prevent saturation of the dissolution medium. At predetermined time points, aliquots were withdrawn and analyzed for drug content by measuring the dissolution medium's absorbance at the corresponding maximum wavelength (λmax) using a UV-spectrometer (UV-1800, Shimadzu, Japan). The cumulative percentage release of Mesalamine was calculated over the sampling times by constructing a Beer-Lambert's calibration curve in the respective medium. The study was conducted in triplicate, and the mean cumulative percentage of drug release and standard deviation were calculated and plotted against time.

**(B) Preparation of simulated colonic fluids**

Male albino rats (180-200 gm) from the Institutional Animal House were employed to obtain cecal contents. The rats were housed in clean cages with sterilized bedding and maintained under controlled temperature (22±2°C), humidity (55±5% RH), and a 12:12 hr light-dark cycle. After acclimatization for 7 days, the animals were fed a standard diet and water ad libitum. All animal experiments were conducted per ethical guidelines approved by the CPCSEA, Government of India, followed by ethical clearance granted by the IAEC, bearing registration number 1018/C/06/CPCSEA vide resolution number 03/ 11/IAEC. With modifications, the rat cecal content medium was prepared based on the method by Singh et al. (2021).

Six albino rats with no prior drug treatment were used for in vivo studies. After weighing, they were maintained on a normal diet. They administered an aqueous dispersion of guar gum and pectin–chitosan mixture (3:1) 1 mL each of 2% w/v strength for 7 days to induce polymer degradation enzymes. Thirty minutes before the study, each rat was humanely euthanized, and the abdomen was opened. The ligated cecum was dissected and immediately transferred into phosphate-buffered saline (pH 6.8) bubbled with $CO_2$.

To make a Simulated Colonic Fluid of 4% w/v dilution, the cecal contents were weighed, pooled, and suspended in Phosphate buffer saline. Then, the suspension was filtered, ultrasonicated for 10 minutes in an ice bath, and centrifuged. The supernatant was collected [16, 17].

**(C) *In vitro* drug release study in standard dissolution media with the presence of rat caecal contents**

To assess the susceptibility of the developed mesalamine delivery systems to colonic bacterial enzymes, drug release studies were performed in PBS pH 6.8 with and without rat cecal contents, which mimics human intestinal microflora [18]. The studies employed USP dissolution apparatus 1 (100 rpm, 37°C) with modifications. A 250 ml beaker containing 100 ml PBS was immersed in the apparatus. After completing dissolution in HCl buffer pH 1.2 (2 hr), PBS pH 4.5 (1 hr), and PBS pH 7.4 (2 hr), the baskets with tablets were transferred to PBS pH 6.8 containing 4% w/v rat cecal contents and release was monitored for 12 hours. Samples were withdrawn periodically, filtered (0.45 µm), and assayed spectrophotometrically for Mesalamine at 330nm. Fresh medium was added to maintain sink conditions after each withdrawal. Experiments were conducted in triplicate.

**Drug release kinetics and mechanism:**

The *in vitro* dissolution data was fitted to various kinetic models: zero-order, first-order, Higuchi, and Korsmeyer-Peppas, to study the drug release kinetics and mechanism of drug release from the tablets. The Korsmeyer-Peppas model is preferred when the release mechanism is unknown or multiple phenomena occur [19, 20]:

Korsmeyer and Peppas equation: $Q= Kt^n$

Where Q is the fractional drug release in time.

K=Constant incorporating structural and geometric characteristics of the controlled release device.

n=Diffusional release exponent, indicative of release mechanism.

The drug release mechanisms from tablet formulations can be characterized based on the "n" values obtained from Korsmeyer-Peppas modeling. For the "n" value of 0.5, the release follows a Fickian diffusion mechanism, with the rate dependent on the square root of time. When "n" lies between 0.5 and 1.0, an anomalous transport mechanism governs the release, where the rate varies as a fractional power of time. A value of 1 indicates a Case II transport mechanism characterized by zero-order release kinetics. Lastly, "n" values greater than 1 suggest a Super Case II transport mechanism, with the rate exhibiting a higher time dependence compared to anomalous transport. The best-fit model was determined statistically by employing a comparison of correlation coefficients. The preparation of graphs and statistical calculations was carried out with the help of Microsoft Excel® software.

**Stability study**

The optimized tablet formulations were accelerated stability tested and evaluated according to the ICH Q1A(R2) guidelines by being stored at 40°C±2°C and 75%±5% relative humidity for 3 months [21, 22]. After this period, the formulation was examined for changes in physical appearance, color, drug content, and drug release profile. After storage, differential scanning calorimetry analysis was also performed on the powdered tablet core.

## *RESULTS AND DISCUSSION*

**Drug Characterization and Analytical Studies:**

The procured drug mesalamine underwent comprehensive characterization and analytical evaluation. It was identified through melting point determination, UV-Vis spectroscopy, loss on drying, and FTIR spectroscopy.

Mesalamine appears as light tan to pink needle-shaped crystals. Its melting point, determined in triplicate, matched the reported range of 282-285°C, corroborated by a DSC endothermic peak at 284.06°C. The loss on drying test showed only 0.0052% weight loss (≤ 0.5% limit). These values serve as reference points for identifying and characterizing the drug substance.

The FTIR spectra of the drug mesalamine exhibited characteristic bands corresponding to O-H, C-H, C-C, C-O, and aromatic ring vibrations, matching the reference spectra. The following peaks and their interpretation: An O-H stretching mode associated with the hydroxyl group was observed at 3445.01 and 3257.91 $cm^{-1}$(reported range 3600-3200 $cm^{-1}$). A C-H stretch of the aromatic group was seen at 2996.47 $cm^{-1}$(reported peak around 3000 $cm^{-1}$) and 1619.31 $cm^{-1}$ (reported peak at 1619 $cm^{-1}$). C-C stretching modes were present at 1454.39 $cm^{-1}$ and 1492.97 $cm^{-1}$ (reported peaks at 1449 $cm^{-1}$ and 1490 $cm^{-1}$). O-H deformation of the hydroxyl group occurred at 1356.02 $cm^{-1}$ and 1380.13 $cm^{-1}$ (reported peaks at 1355 and 1378 $cm^{-1}$). A C-O stretching mode was observed at 1137.09 $cm^{-1}$ (reported peak at 1131 $cm^{-1}$). Finally, C-H ring deformations of the aromatic group were seen at 685.72, 773.49, and 810.14 $cm^{-1}$ (reported range of 685-808 $cm^{-1}$). These analyses confirmed the identity and purity of the mesalamine drug sample (Figure 1).

UV-Vis spectral analysis was performed in various pH environments using buffer solutions, and maximum wavelength (λmax) values were recorded. Its λmax values were 301 nm in hydrochloric acid buffer pH 1.2, 298 nm in phosphate buffer solution (PBS) pH 4.5, 330 nm in PBS pH 7.4, and PBS pH 6.8

(Figure 2). UV spectrophotometric methods were developed to detect and estimate mesalamine in standard solvents. Calibration curves were prepared by plotting the drug's concentrations in different buffers against their respective absorbance at λmax. The linear relationships confirmed Beer-Lambert law compliance. Regression equations were obtained:

Y = mX + c, Where Y = Absorbance at λmax,

X = Drug concentration (µg/mL)

The high correlation coefficients (R2 ≤ 1) indicated a positive correlation between drug concentration and absorbance. These linear relationships enabled the calculation of the drug amounts in dissolution samples using Microsoft Excel®.

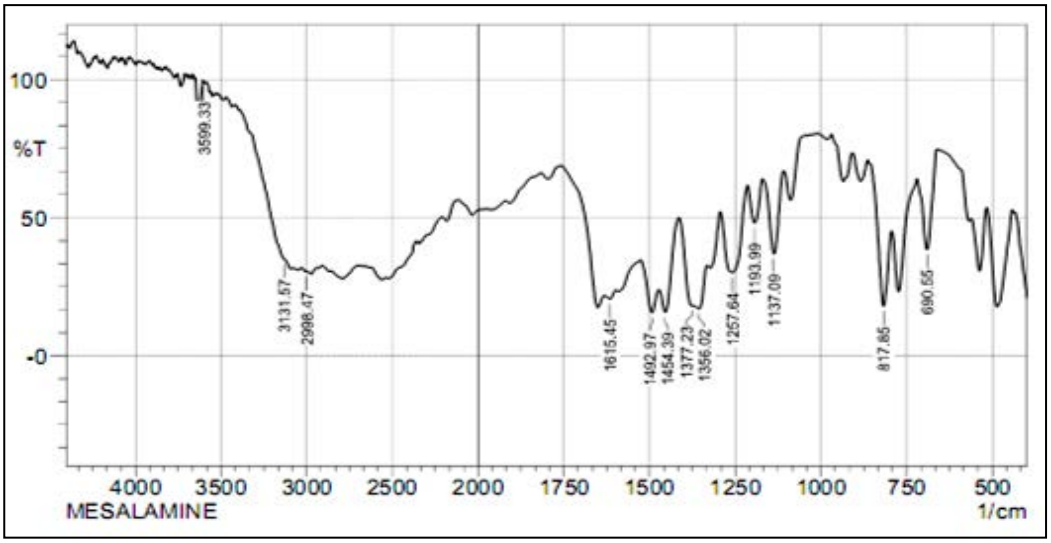


**Figure 1: FTIR spectrum of Mesalamine**

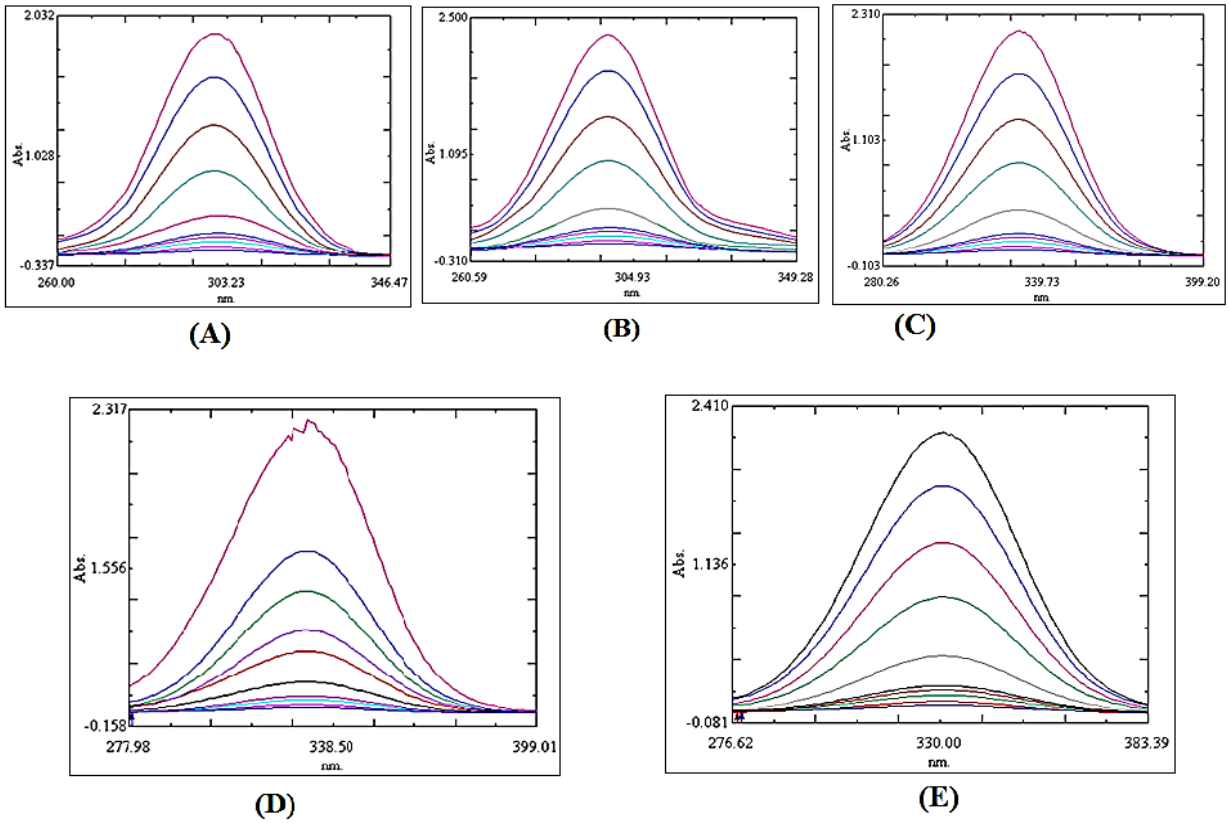


**Figure 2: Overlay spectra of Mesalamine (A) in hydrochloric acid buffer pH 1.2 (B) in PBS pH 4.5 (C) in PBS pH 7.4 (D) in PBS pH 6.8 (E) in PBS pH 6.8 with Pectinex Ultra SPL**

**Drug-polymer compatibility study**

FTIR spectroscopy assessed drug-excipient compatibility. Physical mixtures of drugs and polymers were stored at 40°C±2°C and 75%±5% RH at room temperature for 1 month. FTIR spectra of pure drug, polymers, and their physical mixtures were recorded using Shimadzu FTIR 8400S at 0.5 $cm^{-1}$ resolution. Characteristic peaks were identified and compared using IR solution Version 1.50 software by peak matching technique. The spectra revealed no changes in characteristic peaks, confirming no chemical interactions between drugs and polymers (Table 3 and Figures 3 to 8). Differential scanning calorimetry (DSC) confirmed no interactions between drugs and other formulation components. The DSC thermograms showed sharp endothermic peaks for mesalamine (284.06°C) corresponding to their melting points in crystalline form (Table 4 and Figures 9 to 12). In the physical mixtures of drugs and polymers, characteristic peaks of individual components were observed, indicating their compatibility. The results demonstrated that the preparation methods did not alter the drug's nature within the formulations.

**Table 3: FTIR studies for drug-polymer compatibility**

| Samples | Reported Principle bands ($cm^{-1}$) | Observed principle bands ($cm^{-1}$) |
|---|---|---|
| **Mesalamine** | 3600-3200. 3000, 1619, 1449 and 1490, 1355 and1378, 1131, 685-808 | 3445.01, 3257.91, 2996.47, 1619.31, 1454.39 and 1492.97, 1356.02 and 1380.13, 1137.09, 685.72, 773.49, 810.14 |
| **Pectin** | 1398, 1437, 1888, 1922, 2000, 2075, 2211, 2246, 2261, 2367, 2404, 2481 | 1395.56, 1436.07, 1888.39, 1923.11, 1999.30, 2074.53, 2213.41, 2247.17, 2364.83, 2403.41, 2492.14 |
| **Chitosan** | 1130, 1690, 2376, 3630 | 1130.33, 1688.75, 2376.40, 3628.26 |
| **Guar gum** | 1203, 1397, 1439, 1888, 1928, 2011, 2058, 2243, 2297, 2323 | 1202.67, 1394.59, 1437.03, 1886.46, 1926.97, 2010.88, 2059.10, 2240.42, 2278.03, 2298.28, 2322.39 |
| **HPMC K4M** | 595, 655, 950, 11459, 1325, 1360, 1455, 1645, 2055, 2916, 3470 | 596.00, 651.94. 948.98, 1143.79, 1323.17, 1361.74, 1452.40, 1645.28, 2054.19, 2916.37, 3468.01 |
| **Ethyl Cellulose** | 575, 882, 919, 1057, 1063, 1110, 1280, 1310, 1378, 1402, 1443, 1631, 1751, 2977, 3475, | 573.85, 883.44, 920.08, 1056.07, 1061.86, 1110.08, 1277.90, 1309.72, 1374.34, 1402.31, 1443.78, 1627.99, 1749.51, 2975.33, 3474.91 |
| **Eudragit®S100** | 1140, 1388, 1435, 1746 | 1139.01, 1388.81, 1436.07, 1744.69 |
| **Note:** The IR characteristic absorption bands of physical mixtures of drugs and polymers were found to be identical with its pure drug and polymers. No such additional peaks were observed in the spectrum of physical mixtures. | | |

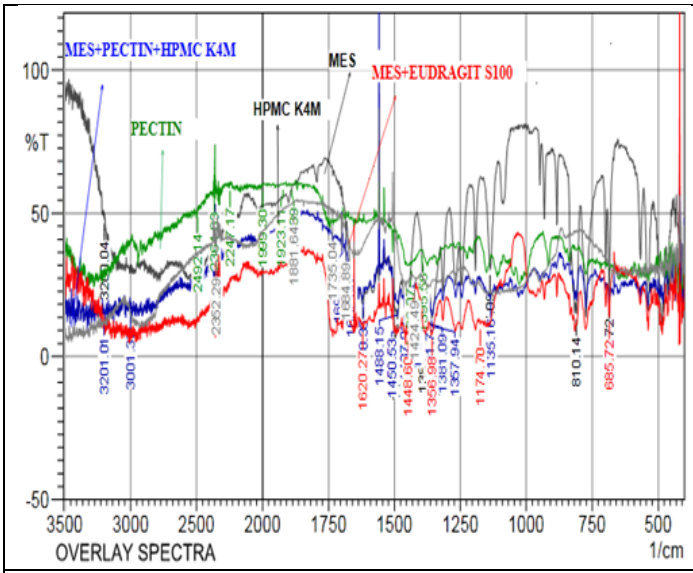


Figure 3: FTIR overlay spectra of Mesalamine, Pectin, HPMC K4M; Mesalamine with Pectin and HPMC K4M; Mesalamine and Eudragit® S100 physical mixtures

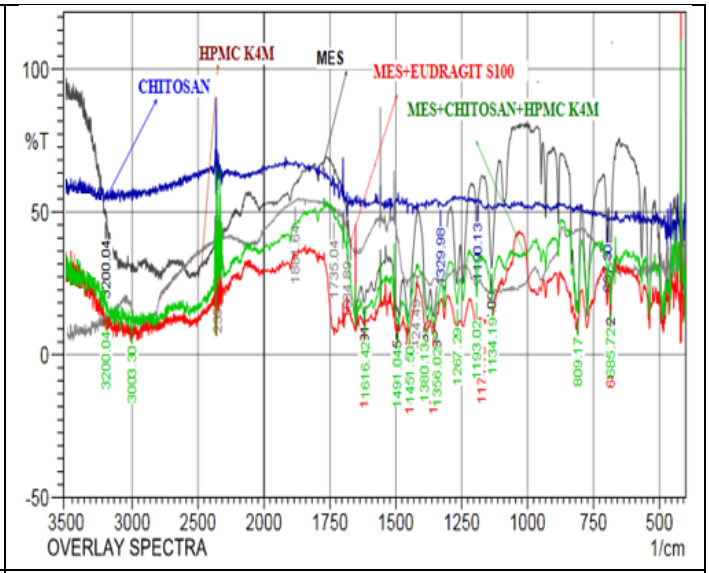


Figure 4: FTIR overlay spectra of Mesalamine, Chitosan, HPMC K4M; Mesalamine with Chitosan and HPMC K4M; Mesalamine and Eudragit® S100 physical mixtures

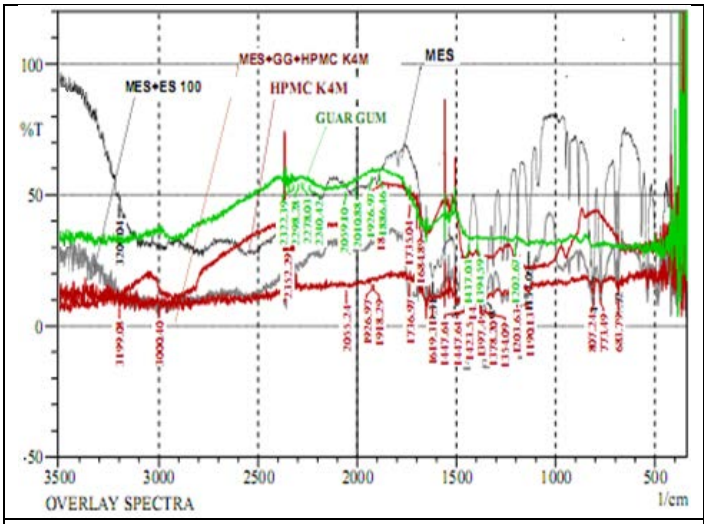


Figure 5: FTIR overlay spectra of Mesalamine, Guar gum, HPMC K4M; Mesalamine with Guar gum and HPMC; Mesalamine and Eudragit® S100 physical mixtures

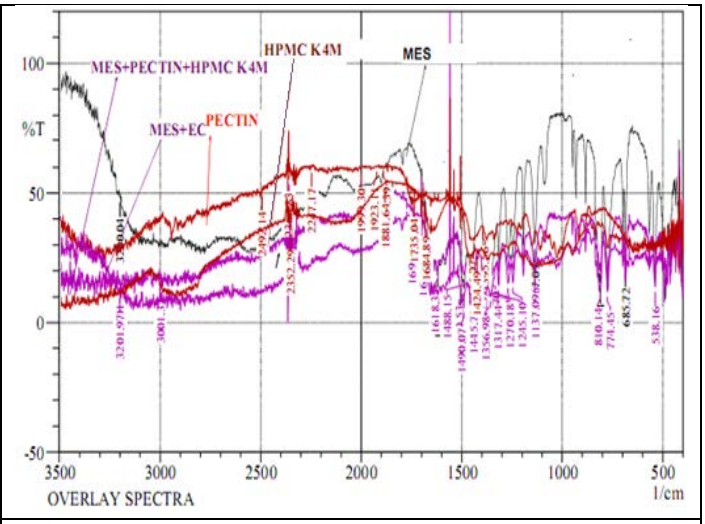


Figure 6: FTIR overlay spectra of Mesalamine, Pectin, HPMC K4M; Mesalamine with Pectin and HPMC K4M; Mesalamine and Ethyl cellulose physical mixtures

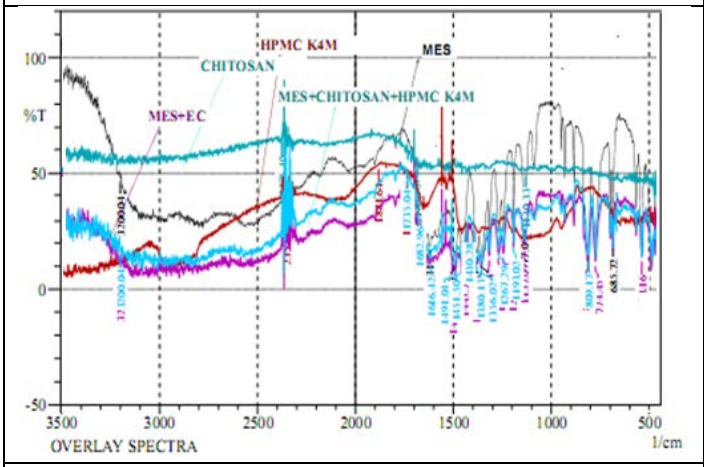


Figure 7: FTIR overlay spectra of Mesalamine, Chitosan, HPMC K4M; Mesalamine with Chitosan and HPMC K4M; Mesalamine and Ethyl cellulose physical mixtures

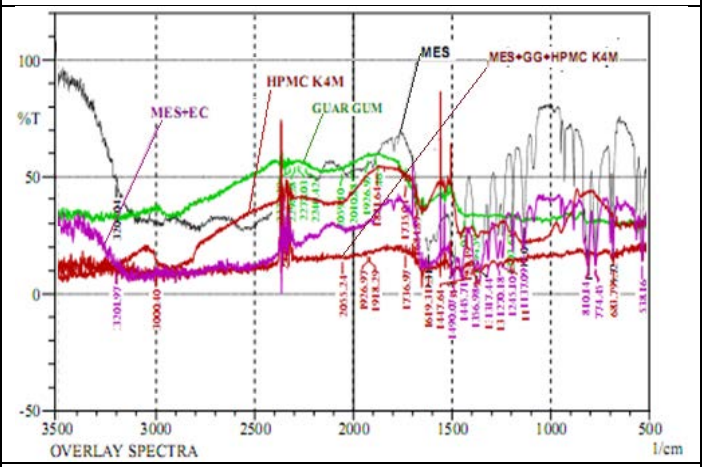


Figure 8: FTIR overlay spectra of Mesalamine, Guar gum, HPMC K4M; Mesalamine with Guar gum and HPMC K4M; Mesalamine and Ethyl cellulose physical mixtures

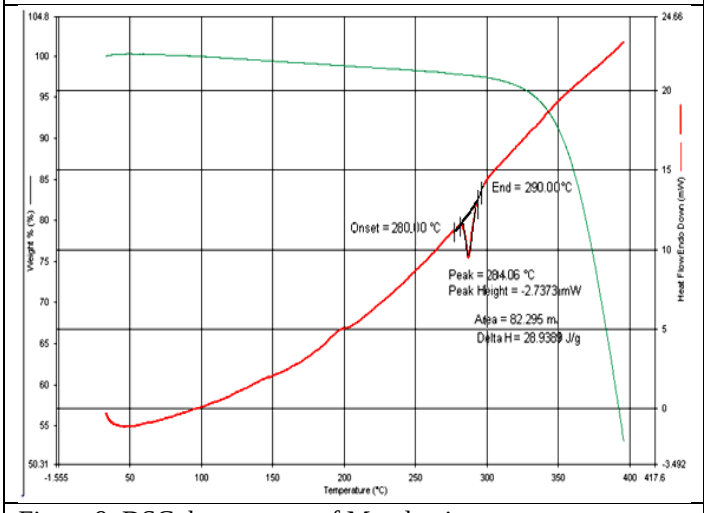


Figure 9: DSC thermogram of Mesalamine

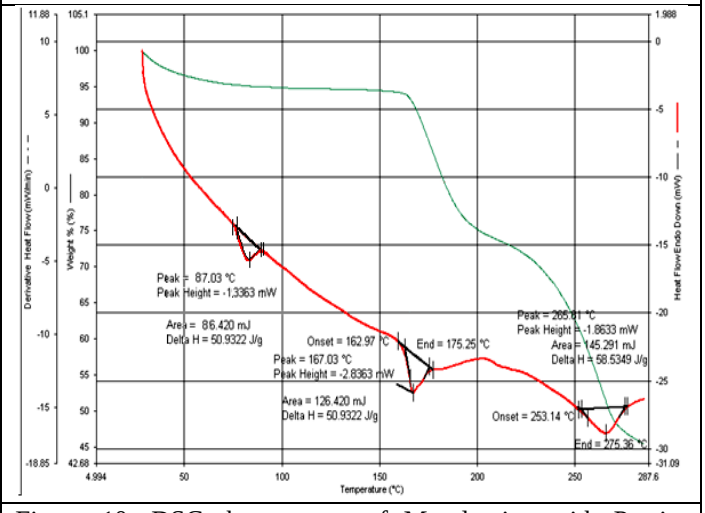


Figure 10: DSC thermogram of Mesalamine with Pectin, HPMC K4M, and Eudragit S100

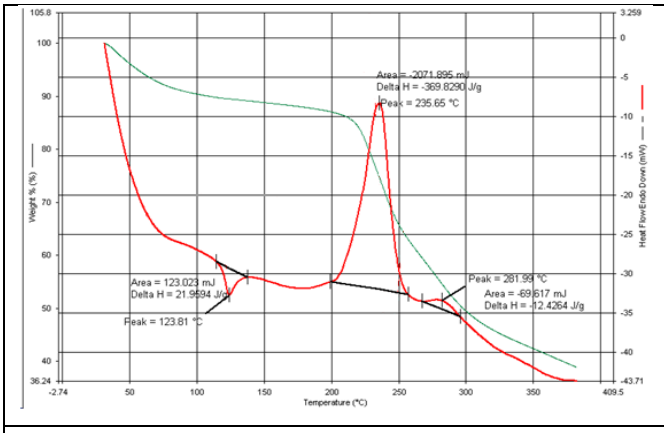


Figure 11: DSC thermogram of Mesalamine with Chitosan, HPMC K4M, and Eudragit 100

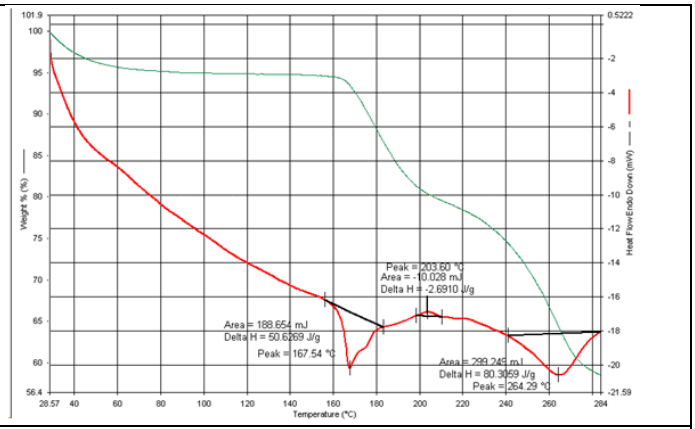


Figure 12: DSC thermogram of Mesalamine with Guar gum, HPMC-K4M, and Eudragit S100

**Table 4: DSC studies for drug-polymer compatibility studies and peak values (Melting point) observed**

| S. No. | Samples | Reported peak value (MP range in °C) | Observed peak value (MP in °C) |
|---|---|---|---|
| 1 | Mesalamine | 280-285°C | 284.06°C |
| 2 | Guar gum | 119.65°C | 124.41 |
| 3 | HPMC K4M | 207.47°C | 207.47 |
| 4 | Chitosan | 75-90°C ; Glass transition temperature 80-93°C | 81.02 |
| 5 | Pectin | 80-85°C | 80.58 |
| 6 | Eudragit®S100 | Glass transition temperature 215°C | 204.01 |
| 7 | Ethyl Cellulose | 160–210°C | 174.59 |
| **Note:** The peak values of drug(s) and polymer(s) in the formulation or physical mixtures of drug and polymers were found to be almost similar to those reported in the thermogram of individual drug and polymer. | | | |

**Formulation and Development of Colon targeted Mesalamine Matrix Tablets**

Matrix tablets were prepared using the wet granulation technique to effectively deliver mesalamine. Granular properties like bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose designated good flow characteristics. Weight variation, hardness (5.3-5.6 kg/cm$^2$), diameter, thickness, and friability (0.256-0.388%) were within acceptable limits. Drug content estimation revealed 96.44 - 98.84% labeled mesalamine (Table 5). The matrix tablets containing varying concentrations of natural polysaccharides (guar gum, pectin, chitosan) and HPMC K4M were coated with 5% w/v Eudragit S100 and Ethyl cellulose solutions separately. The coating thickness ranged from 0.057-0.060 mm, indicating uniform coating (Tables 6 & 7).

***In vitro* drug release study from matrix tablets**

In vitro drug release studies were performed to assess the capability of the prepared mesalamine matrix tablets to control drug release in simulated gastrointestinal environments. The dissolution tests carried out in standard buffer solutions as simulated media without and with rat cecal contents, feigning the GI transit by altering pH and media composition at specific time intervals. Initially, drug release from pectin/HPMC K4M (M1-M3), chitosan/HPMC K4M (M4-M6), and guar gum/ HPMC K4M (M7-M9) matrix tablets was assessed. Formulations M3, M6, and M7 demonstrated the best ability to restrict drug release to 19.03%, 23.98%, and 24.06%, respectively, in simulated gastric fluid and 30.97%, 38.05% and 30.87%, respectively, simulated intestinal fluids (Figure 13). The formulations were coated with pH-sensitive polymers, Eudragit S100 and Ethyl cellulose, to enhance colon targeting further. The ethyl cellulose-coated formulations MC3, MC6, and MC7 exhibited delayed drug release in simulated gastric and intestinal environments, with less than 2.1% release after 3 hours and less than 21.467% after 5 hours. However, in simulated colonic fluid, these formulations achieved significant drug release of 77.81%, 70.65%, and 54.19%, respectively, after 12

hours (Figure 15). Eudragit S100-coated tablets (optimized formulations ME3, ME6, ME7) exhibited superior protection in upper GIT, with minimal drug release (<5.2%) after 5 hours (Figure 14), monitored by measured release in simulated colonic fluid (46.9% to 71.1% after 12 hours). Dissolution studies in the presence of rat cecal contents (4% w/v) had shown improved drug release from Eudragit S100-coated tablets (optimized formulations ME3, ME6, ME7) in simulated colonic conditions, with 71.2% to 83.5% release after 12 hours, signifying their appropriateness for colonic drug delivery (Figure 16). This indicates successful colon-targeted drug delivery by restricting release in the upper gastrointestinal tract. Compared to ethyl cellulose formulations, Eudragit® S100 formulations demonstrated superior performance in limiting drug release in the upper gastrointestinal tract.

**Table 5: Evaluation parameters of Mesalamine matrix tablets**

| Test parameters | Formulation code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **M1** | **M2** | **M3** | **M4** | **M5** | **M6** | **M7** | **M8** | **M9** |
| **Powder rheology/ Granular properties** | | | | | | | | | |
| **Bulk density (gm/ml)** | 0.368 ±0.013 | 0.373 ±0.017 | 0.383 ±0.011 | 0.371 ±0.014 | 0.359 ±0.006 | 0.366 ±0.006 | 0.371 ±0.011 | 0.383 ±0.014 | 0.378 ±0.013 |
| **Tapped density (gm/ml)** | 0.412 ±0.012 | 0.426 ±0.011 | 0.435 ±0.010 | 0.421 ±0.011 | 0.412 ±0.013 | 0.420 ±0.011 | 0.416 ±0.016 | 0.434 ±0.012 | 0.431 ±0.016 |
| **Carr's index (%)** | 10.7 ±1.79 | 12.3 ±1.85 | 11.9 ±1.67 | 11.8 ±1.84 | 12.8 ±1.78 | 12.7 ±1.72 | 10.8 ±1.14 | 11.9 ±1.75 | 12.2 ±1.63 |
| **Hausner's ratio** | 1.130 ±0.031 | 1.140 ±0.014 | 1.134 ±0.033 | 1.134 ±0.024 | 1.145 ±0.018 | 1.147 ±0.029 | 1.132 ±0.022 | 1.139 ±0.020 | 1.140 ±0.030 |
| **Angle of repose (θ)** | 22.39 ±1.21 | 23.91 ±1.20 | 23.60 ±1.31 | 23.21 ±1.25 | 20.81 ±1.85 | 23.12 ±1.59 | 24.48 ±0.76 | 23.98 ±0.87 | 23.17 ±0.67 |
| **Compression characteristics/ Tabletting properties** | | | | | | | | | |
| **Hardness ($kg/cm^2$)** | 5.4 ±0.35 | 5.5 ±0.41 | 5.6 ±0.36 | 5.4 ±0.81 | 5.4 ±0.62 | 5.6 ±0.48 | 5.3 ±.0.80 | 5.3 ±0.63 | 5.5 ±0.55 |
| **Diameter (in mm)** | 9.571 ±0.013 | 9.569 ±0.012 | 9.567 ±0.012 | 9.561 ±0.011 | 9.541 ±0.012 | 9.566 ±0.012 | 9.567 ±0.011 | 9.564 ±0.013 | 9.568 ±0.012 |
| **Thickness (in mm)** | 5.410 ±0.141 | 5.396 ±0.144 | 5.411 ±0.142 | 5.316 ±0.144 | 5.316 ±0.142 | 5.318 ±0.143 | 5.409 ±0.144 | 5.410 ±0.144 | 5.412 ±0.144 |
| **Friability (%)** | 0.304 ±0.024 | 0.256 ±0.022 | 0.271 ±0.023 | 0.388 ±0.022 | 0.347 ±0.022 | 0.296 ±0.024 | 0.333 ±0.021 | 0.321 ±0.022 | 0.299 ±0.021 |
| **Weight variation test** | Passes | Passes | Passes | Passes | Passes | Passes | Passes | Passes | Passes |
| **Drug content (mg)** | 97.01 ±0.30 | 97.89 ±0.53 | 98.84 ±0.38 | 97.11 ±0.42 | 96.99 ±0.32 | 98.79 ±0.56 | 98.82 ±0.42 | 96.56 ±0.62 | 96.44 ±0.38 |

**All values are expressed as mean ± SD, n=6**

**Table 6: Evaluation parameters of Mesalamine matrix tablets coated with 5% Eudragit® S100**

| Test parameters | Formulation code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **ME1** | **ME2** | **ME3** | **ME4** | **ME5** | **ME6** | **ME7** | **ME8** | **ME9** |
| **Diameter (in mm)** | 9.687 ±0.11 | 9.683 ±0.10 | 9.677 ±0.12 | 9.685 ±0.12 | 9.659 ±0.11 | 9.676 ±0.12 | 9.677 ±0.11 | 9.686 ±0.10 | 9.684 ±0.12 |
| **Thickness (in mm)** | 5.526 ±0.11 | 5.514 ±0.12 | 5.529 ±0.12 | 5.438 ±0.12 | 5.436 ±0.12 | 5.434 ±0.11 | 5.523 ±0.11 | 5.528 ±0.12 | 5.532 ±0.13 |
| **Coating Thickness (in mm)** | 0.058 ±0.02 | 0.059 ±0.002 | 0.059 ±0.01 | 0.061 ±0.01 | 0.060 ±0.01 | 0.058 ±0.02 | 0.057 ±0.02 | 0.059 ±0.02 | 0.060 ±0.01 |
| **Increase in Diameter (in mm)** | 0.056 ±0.03 | 0.057 ±0.02 | 0.055 ±0.02 | 0.062 ±0.02 | 0.059 ±0.02 | 0.055 ±0.02 | 0.055 ±0.02 | 0.061 ±0.02 | 0.058 ±0.02 |

***All values are expressed as mean ± SD, n=6**

**Table 7: Evaluation parameters of Mesalamine matrix tablets coated with 5% ethyl cellulose.**

| Test parameters | Formulation code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | MC1 | MC2 | MC3 | MC4 | MC5 | MC6 | MC7 | MC8 | MC9 |
| Diameter (in mm) | 9.687 ±0.10 | 9.687 ±0.12 | 9.685 ±0.10 | 9.681 ±0.11 | 9.661 ±0.12 | 9.696 ±0.12 | 9.693 ±0.12 | 9.686 ±0.10 | 9.688 ±0.11 |
| Thickness (in mm) | 5.530 ±0.01 | 5.518 ±0.02 | 5.533 ±0.01 | 5.44 ±0.01 | 5.44 ±0.02 | 5.444 ±0.02 | 5.531 ±0.03 | 5.528 ±0.03 | 5.536 ±0.02 |
| Coating Thickness (in mm) | 0.060 ±0.02 | 0.061 ±0.02 | 0.061 ±0.02 | 0.062 ±0.02 | 0.062 ±0.02 | 0.063 ±0.02 | 0.061 ±0.02 | 0.059 ±0.02 | 0.062 ±0.02 |
| Increase in Diameter (in mm) | 0.058 ±0.02 | 0.059 ±0.02 | 0.059 ±0.02 | 0.060 ±0.02 | 0.060 ±0.02 | 0.065 ±0.02 | 0.063 ±0.02 | 0.058 ±0.02 | 0.060 ±0.02 |

***All values are stated as mean ± SD, n=6**

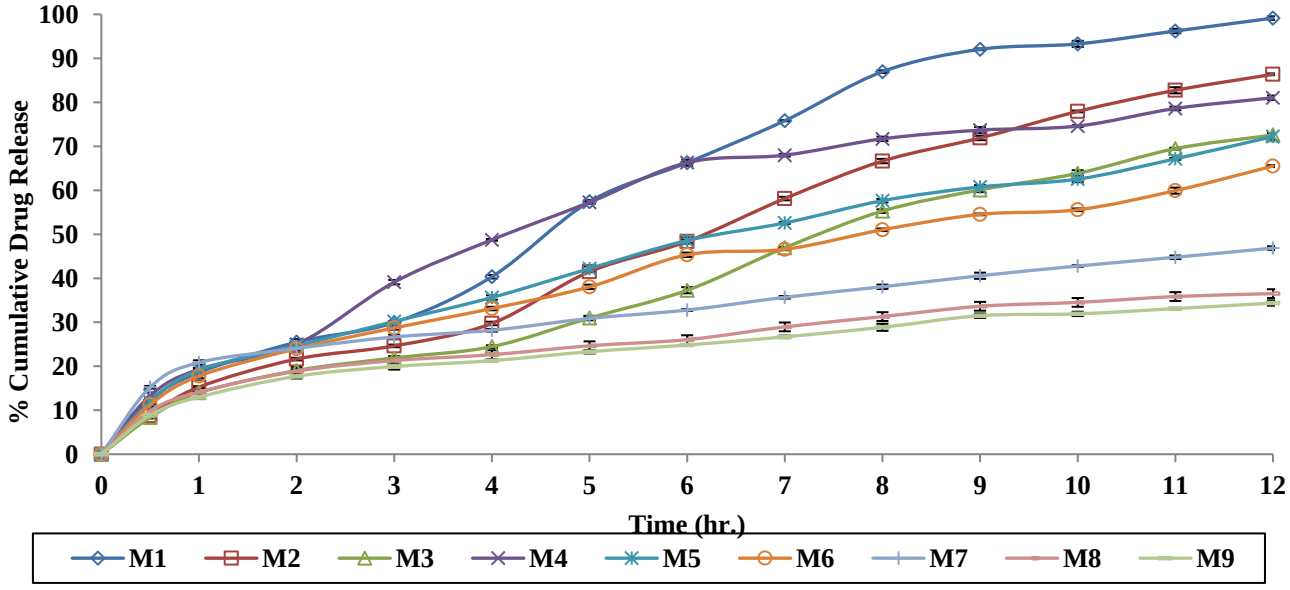


**Figure 13: *In vitro* drug release data of Mesalamine matrix tablets in standard buffer solutions**

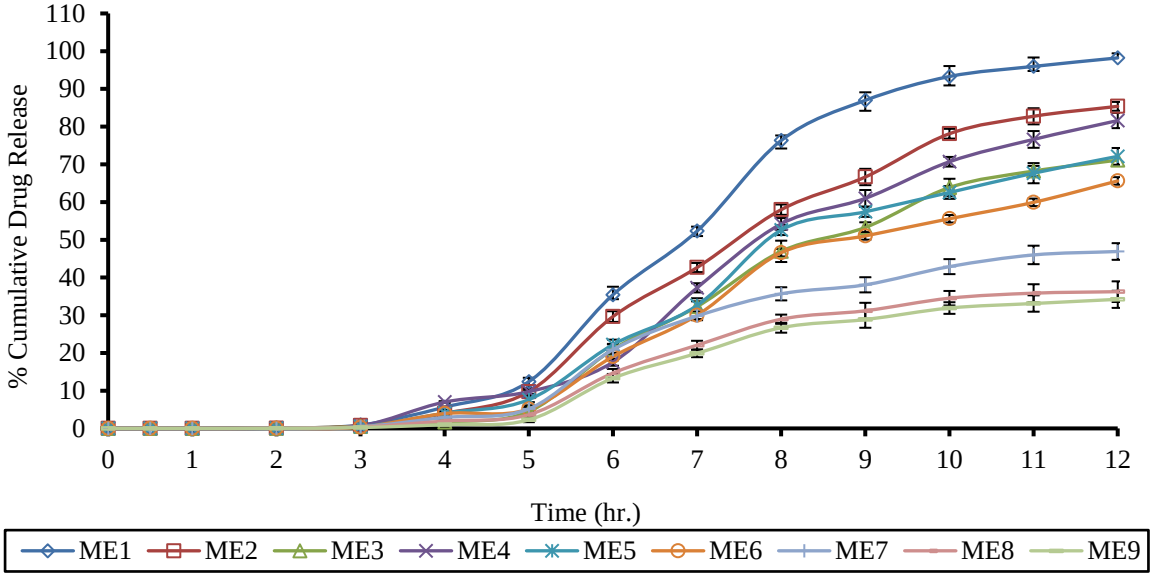


**Figure 14: *In vitro* drug release data of Mesalamine matrix tablets coated with 5% Eudragit® S100 in standard buffer solutions**

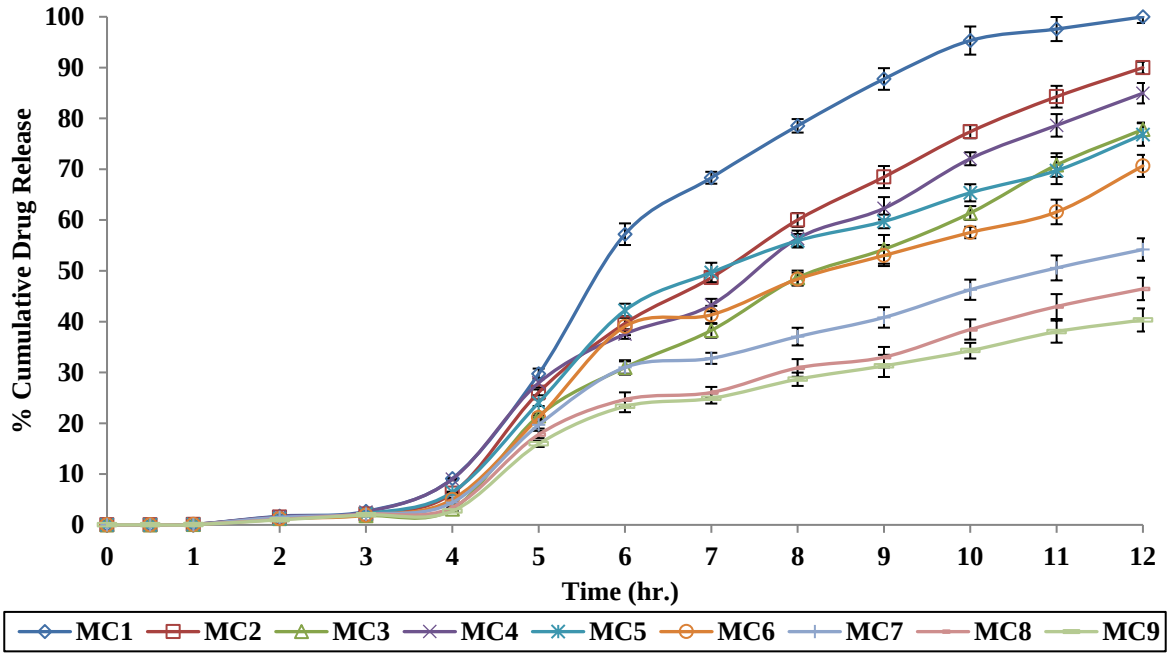


**Figure 15: *In vitro* drug release data of Mesalamine matrix tablets coated with 5% ethyl cellulose in standard buffer solutions**

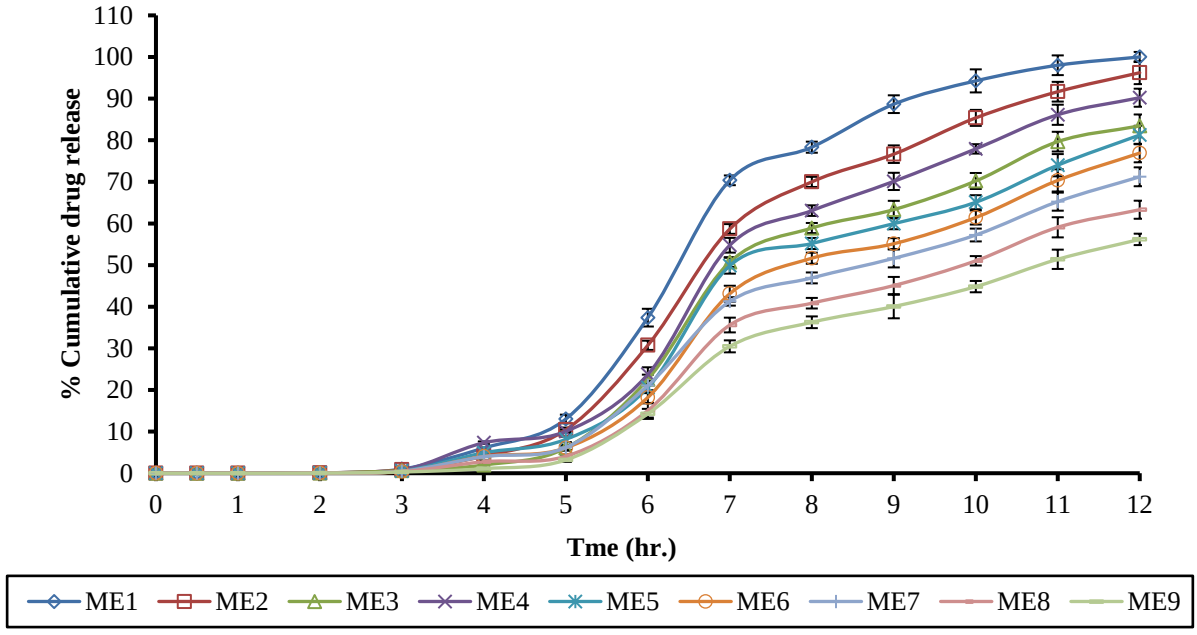


**Figure 16: *In vitro* drug release data of Mesalamine matrix tablets coated with 5% Eudragit® S100 in standard buffer solutions with 4% rat cecal contents**

**Drug release mechanisms and kinetics**

The experimental data was fitted into different kinetic models like zero order, first order, Higuchi's, and Korsmeyer-Peppas equations to illuminate the drug release pattern and mechanisms (Table 8). The correlation coefficients demonstrated an adequate fit to zero-order kinetics for all formulations. Additionally, the release data followed Higuchi's equation, indicating a diffusion-controlled release mechanism. The release exponent (n) values obtained from the Korsmeyer-Peppas model were in the range of $0.5 < n < 1.0$ for uncoated formulations M3, M6, and M7, suggesting an anomalous transport mechanism. However, for the coated formulations ME3, ME6, ME7, MC3, MC6, and MC7, the n values were close to 1, indicating a super case-II transport or zero-order release mechanism.

**Table 8: Dissolution kinetics of optimized Mesalamine matrix tablet formulations**

| Optimized Formulation Code | Zero Order ($R^2$) | First Order ($R^2$) | Higuchi ($R^2$) | Korsmeyer's Plot ($R^2$) | Korsmeyer's Exponent "n" |
|---|---|---|---|---|---|
| **M3** | 0.986 | 0.696 | 0.935 | 0.699 | 0.940 |
| **M6** | 0.951 | 0.563 | 0.994 | 0.594 | 0.823 |
| **M7** | 0.875 | 0.442 | 0.974 | 0.447 | 0.636 |
| **ME3** | 0.908 | 0.761 | 0.739 | 0.932 | 1.901 |
| **ME6** | 0.913 | 0.746 | 0.751 | 0.917 | 1.896 |
| **ME7** | 0.921 | 0.732 | 0.780 | 0.905 | 1.728 |
| **MC3** | 0.981 | 0.817 | 0.909 | 0.927 | 1.591 |
| **MC6** | 0.953 | 0.788 | 0.917 | 0.920 | 1.558 |
| **MC7** | 0.930 | 0.758 | 0.929 | 0.899 | 1.395 |

**Table 9: Stability study data for optimized Mesalamine matrix tablet formulations at 40°C±2°C/ 75%±5% RH for 3 months**

| Parameter | Formulation code | Initial | 1 month | 2 month | 3 month |
|---|---|---|---|---|---|
| **Appearance** | ME3 | Reddish brown, round shaped enteric coated plain on both sides | No change | No change | No change |
| | ME6 | | No change | No change | No change |
| | ME7 | | No change | pale brownish | pale brownish |
| **Avg. Wt. (mg)** | ME3 | 420±1.5 | 419±1.45 | 422±1.39 | 420±1.51 |
| | ME6 | 420±1.38 | 420±1.5 | 420±1.62 | 420±1.23 |
| | ME7 | 420±1.37 | 420±1.5 | 421±1.34 | 419±1.45 |
| **Hardness ($kg/cm^2$)** | ME3 | 5.6±0.4 | 5.5±0.35 | 5.5±0.42 | 5.5±0.37 |
| | ME6 | 5.6±0.48 | 5.6±0.35 | 5.5±0.24 | 5.5±0.64 |
| | ME7 | 5.3±.0.8 | 5.2±.0.18 | 5.2±.0.15 | 5.3±.0.07 |
| **Drug content (mg)** | ME3 | 98.84±0.38 | 98.02±0.33 | 97.86±0.34 | 97.53±0.32 |
| | ME6 | 98.79±0.56 | 97.68±0.27 | 97.68±0.31 | 97.84±0.32 |
| | ME7 | 98.82±0.42 | 98.02±0.23 | 97.76±0.29 | 97.88±0.27 |

**All values are stated as mean ± SD, n= 3**

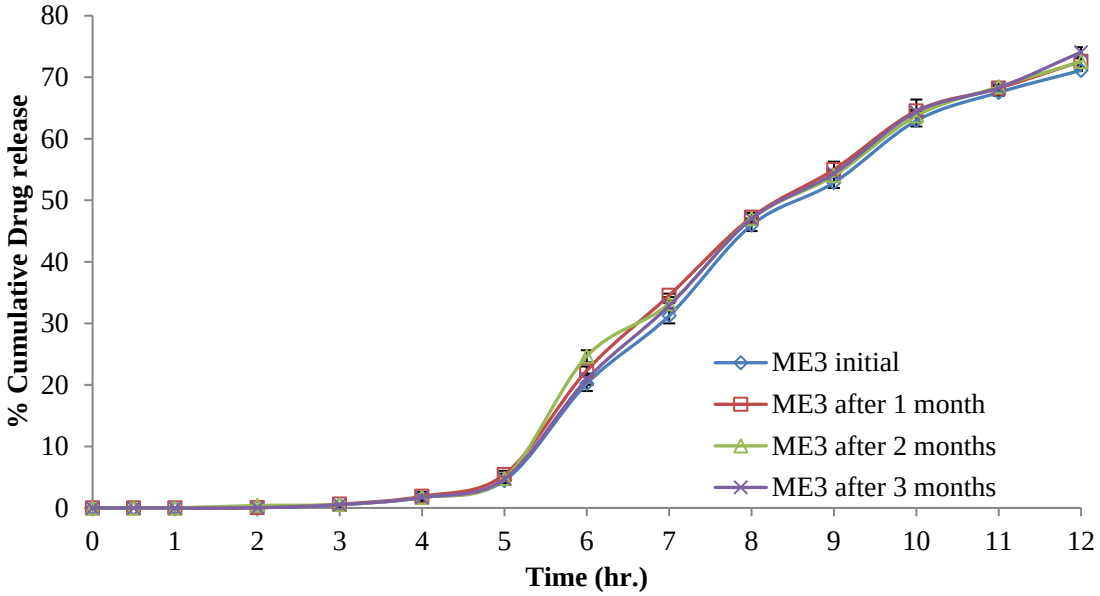


**Figure 17: *In vitro* drug release profiles of optimized matrix tablets of Mesalamine enteric coated with 5% Eudrgit® S100 (ME3) before and during stability studies**

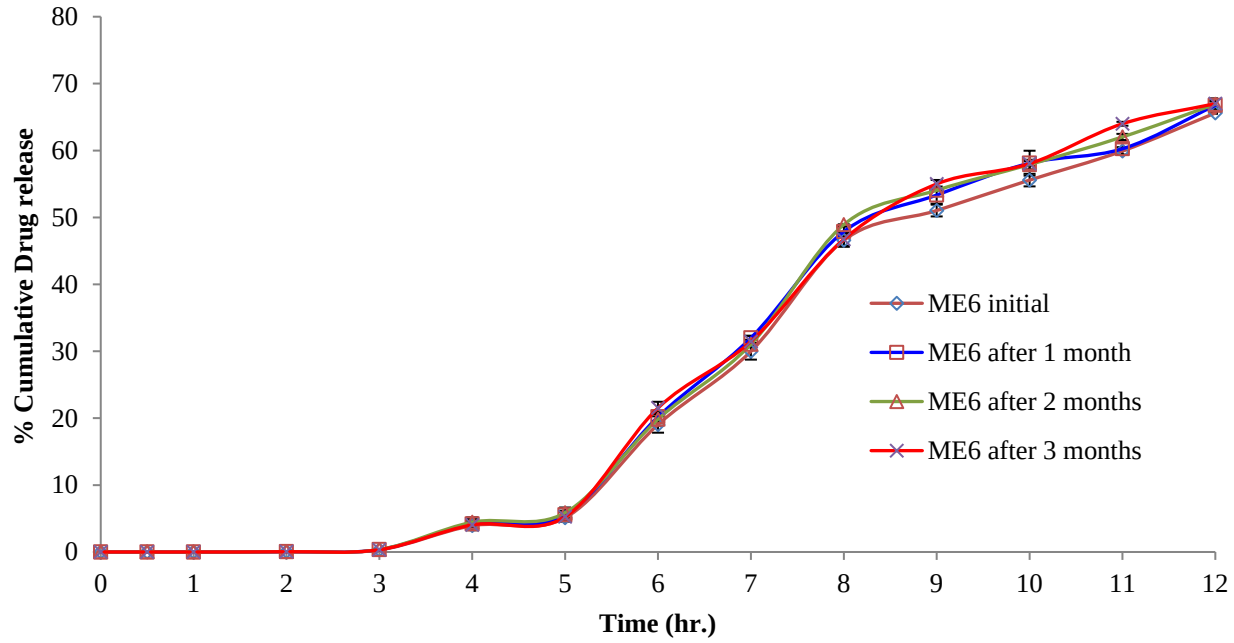


**Figure 18: *In vitro* drug release profiles of optimized matrix tablets of Mesalamine enteric coated with 5% Eudrgit® S100 (ME6) before and during stability studies**

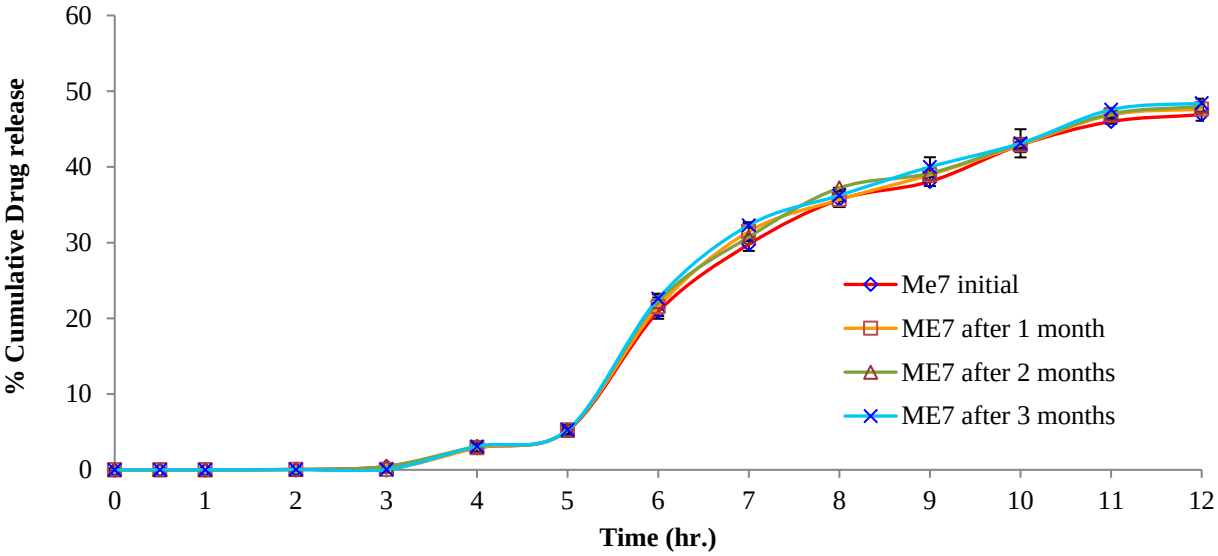


**Figure 19: *In vitro* drug release profiles of optimized matrix tablets of Mesalamine enteric coated with 5% Eudrgit® S100 (ME7) before and during stability studies**

**Stability studies**

To assess the long-term stability (2 years) of the optimized formulations (ME3, ME6, and ME7) for colon-targeted delivery of mesalamine, accelerated stability studies were conducted at 40°±2°C and 75%±5% relative humidity for 3 months, following ICH Q1A(R2) guidelines and WHO recommendations for global markets. No physical appearance change was detected after the storage period was completed. The formulations were assessed for physical parameters, drug content, *in vitro* drug release, and DSC studies. Insignificant changes in physical appearance, weight variation, drug, and drug content (Table 9) indicated optimum stability and a minimum shelf life of 2 years.

***CONCLUSION***

The research aimed to develop novel colon-targeted mesalamine (5-aminosalicylic acid) matrix tablet formulations for treating inflammatory bowel diseases like ulcerative colitis and Crohn's disease. Mesalamine matrix tablets were prepared by wet granulation using pH-sensitive polymer (HPMC K4M) and biodegradable polymers (pectin, chitosan, guar gum). FTIR and

DSC studies confirmed compatibility between mesalamine and polymers. The optimized uncoated formulations (M3, M6, and M7) adequately restricted drug release in simulated gastric and intestinal fluids. These formulations were further enteric-coated with Eudragit S100 and ethyl cellulose for enhanced upper GIT protection. The Eudragit S100-coated formulations ME3, ME6, and ME7 exhibited a 2-hour lag time and drug release around 4.46%, 5.12 %, and 5.18%, respectively, in SGF and SIF up to 5 hours. However, in SCF containing rat cecal contents (4% w/v), these formulations demonstrated enhanced drug release (71% to 83% in 12 hours) due to colonic enzymes' biodegradation of polymeric matrices. Drug release kinetics study indicated anomalous transport or super case-II transport mechanisms for the optimized formulations. Accelerated stability studies at 40°C±2°C/75%±5% RH for 3 months revealed no significant changes in appearance, drug content, and dissolution profiles, suggesting adequate stability. These colon-targeted formulations can improve therapeutic effectiveness and reduce systemic side effects in irritable bowel diseases. However, further in vivo studies are recommended to establish their clinical efficacy and safety.

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***FINANCIAL ASSISTANCE***

Nil

***CONFLICT OF INTEREST***

The authors declare no conflict of interest

***AUTHOR CONTRIBUTION***

This research endeavor was conducted under the esteemed guidance of Padala Narasimha Murthy, who graciously provided the requisite facilities. Prasanta Kumar Choudhury skillfully executed the formulation and development of the matrix tablets and the article. Gourishyam Pasa, Shilpa Sahu, Poonam Sahu, and Renuka Verma made valuable contributions by meticulously analyzing all the experimental results and preparing the corresponding data. All authors critically reviewed the final manuscript and provided necessary corrections, ensuring its accuracy and coherence.

***REFERENCES***

[1] Dahlhamer JM, Zammitti EP, Ward BW, Wheaton AG, Croft JB. Prevalence of Inflammatory Bowel Disease Among Adults Aged ≥18 Years — United States, 2015. *Morbidity and Mortality Weekly Report*, **65(42)**,1166–1169 (2016)

[2] Maroni A, Zema L, Cerea M, Sangalli ME. Colon-targeted drug delivery systems: Current perspectives. *Journal of Drug Targeting*, **29(4)**, 359-372 (2021)

[3] Amidon S, Brown JE, Dave VS. Colon-targeted oral drug delivery systems: Design trends and approaches. *AAPS PharmSciTech*, **16(4)**, 731-741 (2015)

[4] Krishnaiah YSR. Colon-specific drug delivery systems: A review on primary and novel approaches. *Current Drug Delivery*, **17(3)**, 241-260 (2020)

[5] Roberto AP, Cristina M, José ML. Recent advances in colon drug delivery systems. *Journal of Controlled Release*, **327**, 703-724 (2020)

[6] Aline M dos S, Suzana GC, Andréia BM, Rafael MS, Maria PDG, Marlus C. Oral delivery of micro/nanoparticulate systems based on natural polysaccharides for intestinal diseases therapy: Challenges, advances and future perspectives. *Journal of Controlled Release*, **334**, 353-366 (2021)

[7] Uwah TO, Akpabio EI, Effiong D. Plants as pharmaceutical excipients in oral sustained drug delivery systems: A review. *Journal of Applied Pharmaceutical Research*, **9(3)**, 26-38 (2021)

[8] Sen S, Das M, Ghosh B, Ghosh LK. Design, development and in vitro evaluation of sequentially optimized mesalamine tablets for optimum colonic delivery. *Future Journal of Pharmaceutical Sciences*, **4 (1)**, 8-13 (2018)

[9] Nassar MY, El-Shahat MF, Khalile SM. Structure investigation of mesalazine drug using thermal analyses, mass spectrometry, DFT calculations, and NBO analysis. *Journal of Thermal Analysis and Calorimetry*, **117**, 463–471 (2014)

[10] Theodore EL, Alvaro FL, Marsia G, Agus BNP, Ario BJ, Pietradewi H. Thiolated pectin-chitosan composites:

Potential mucoadhesive drug delivery system with selective cytotoxicity towards colorectal cancer. *International Journal of Biological Macromolecules*, **225**, 1-12 (2023)

[11] Mohamed HF, Mohammed F A, Amer S A, Ahmed A, Bjad KA, Alhussain HA, Hesham MT, El-Sayed K, Doaa AH. Design-of-experiment approach to quantify the effect of nano-sized silica on tableting properties of microcrystalline cellulose to facilitate direct compression tableting of binary blend containing a low-dose drug. *Journal of Drug Delivery Science and Technology*, **68**, 03127 (2022)

[12] Yufeng Z, Siu KW, Wei L, Fang G, Xiaoyu Y, Zhong Z. Population pharmacokinetics and IVIVC for mesalazine enteric-coated tablets. *Journal of Controlled Release*, **346**, 275-288 (2022)

[13] Ganguly D, Ghosh S, Chakraborty P, Mitra S, Chatterjee S, Panja S, Choudhury A. A brief review on recent advancement of tablet coating technology. *Journal of Applied Pharmaceutical Research*, **10(1)**, 07-14 (2022)

[14] Ali M, Kohli K. In vitro/in vivo evaluation of HPMC/alginate based extended-release matrix tablets of cefpodoxime proxetil. *International Journal of Biological Macromolecules*, **89**, 434-441 (2016)

[15] Yu Z, Xiaohong Z, Qingchun D, Yamin F, Xinli H. Hydrogen-rich saline ameliorates lung injury associated with cecal ligation and puncture-induced sepsis in rats. *Experimental and Molecular Pathology*, **98 (2)**, 2015, 268-276 (2015)

[16] Singh A, Mandal UK, Narang RK. Development and characterization of enteric coated pectin pellets containing mesalamine and Saccharomyces boulardii for specific inflamed colon: In vitro and in vivo evaluation. *Journal of Drug Delivery Science and Technology*, **62**, 102393 (2021)

[17] Moutaharrik S, Maroni A, Neut C, Dubuquoy C, Dubuquoy L, Foppoli A, Cerea M, Palugan L, Siepmann F, Siepmann J, Gazzaniga A. In vitro and in vivo evaluation of a pH-, microbiota- and time-based oral delivery platform for colonic release, *European Journal of Pharmaceutics and Biopharmaceutics*, **183**, 13-23 (2023)

[18] Tao Lu, Timo LM. A novel kinetic model to describe the ultra-fast triggered release of thermosensitive liposomal drug delivery systems. *Journal of Controlled Release*, **324**, 669-678 (2020)

[19] Ch. JM, Mishra S, Srivastava PK. In vitro release kinetics of graft matrices from Lannea coromandelica (Houtt) gum for treatment of colonic diseases by 5-ASA. *International Journal of Biological Macromolecules*, **149**, 908-920 (2020)

[20] Deshmukh PR, Gaikwad VL, Tamane PK, Mahadik KR, Purohit RN. Development of stability-indicating HPLC method and accelerated stability studies for osmotic and pulsatile tablet formulations of Clopidogrel Bisulfate. *Journal of Pharmaceutical and Biomedical Analysis*, **165**, 346-356 (2019)

[21] Vagare RS. Microbial triggered colon targeted compression coated tablets of tenoxicam: formulation and evaluation. *Journal of Drug Delivery & Therapeutics*, **5(1)**, 75-1 (2015)

[22] Omari D, Sallam A, Al-Hmoud H, Iyad R. Modafinil-excipient compatibility study using differential scanning calorimetry. *Journal of Advanced Pharmaceutical Technology and Research*, **14(2)**, 75–81 (2023)