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DESIGN, FORMULATION DEVELOPMENT, OPTIMIZATION, CHARACTERIZATION, AND EVALUATION OF A COLON-TARGETED DRUG DELIVERY SYSTEM OF MESALAMINE

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Abstract:
Background: *Colon-targeted drug delivery systems have attracted considerable attention for the effective management of inflammatory bowel diseases by delivering drugs specifically to the colon while minimizing premature drug release in the upper gastrointestinal tract. The present study aimed to develop and optimize a colon-targeted matrix tablet of Mesalamine using natural polysaccharide polymers.*
Methods: *Mesalamine matrix tablets were formulated using Xanthan gum and Guar gum as release-retarding polymers through the wet granulation technique. A 3^2 full factorial design was employed to optimize the formulation by evaluating the influence of polymer concentrations on swelling behavior and drug release characteristics. The prepared formulations were subjected to preformulation studies, FTIR compatibility analysis, pre- and post-compression evaluation, swelling index determination, in vitro dissolution studies under simulated gastrointestinal conditions, and accelerated stability testing.*
Results: *All formulations exhibited satisfactory flow properties and complied with pharmacopoeial specifications for hardness, friability, weight variation, thickness, and drug content. Swelling studies demonstrated progressive hydration with increasing polymer concentration, resulting in enhanced gel formation and sustained drug release. In vitro dissolution studies showed minimal drug release in simulated gastric (3.53–5.90%) and intestinal (29.82–37.13%) media, while maximum drug release (62.52–69.53%) occurred under simulated colonic conditions within 12 h, confirming effective colon targeting. Statistical optimization identified formulation F3 as the optimized formulation, exhibiting desirable swelling characteristics, controlled drug release, and excellent matrix integrity. Accelerated stability studies conducted at 40 ± 2°C/75 ± 5% RH for six months demonstrated no significant changes in the dissolution profile or physical characteristics of the optimized formulation.*
Conclusion: *The developed Mesalamine colon-targeted matrix tablets successfully achieved site-specific and sustained drug delivery using natural biodegradable polymers. The optimized formulation demonstrated excellent pharmaceutical performance, stability, and colon-specific drug release, suggesting its potential as an effective oral delivery system for the management of ulcerative colitis and other inflammatory bowel diseases.*
Keywords*: Mesalamine; Colon-targeted drug delivery; Matrix tablets; Xanthan gum; Guar gum; 3^2 Full Factorial Design; Controlled drug release; Swelling index; Ulcerative colitis; Inflammatory bowel disease.*

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INTRODUCTION:

Inflammatory bowel disease (IBD) is a chronic, relapsing inflammatory disorder of the gastrointestinal tract that primarily includes ulcerative colitis (UC) and Crohn's disease (CD). These disorders are characterized by recurrent episodes of intestinal inflammation that result in abdominal pain, diarrhea, rectal bleeding, weight loss, and impaired quality of life. The global incidence and prevalence of IBD have increased considerably over the past few decades owing to changes in lifestyle, dietary habits, environmental factors, and genetic predisposition. Ulcerative colitis mainly affects the colonic mucosa, whereas Crohn's disease may involve any part of the gastrointestinal tract. Since inflammation in ulcerative colitis is localized predominantly in the colon, localized drug delivery offers significant therapeutic advantages over conventional systemic administration.

Mesalamine (5-aminosalicylic acid, 5-ASA) is considered the first-line therapeutic agent for the induction and maintenance of remission in patients with mild to moderate ulcerative colitis. The drug exerts its therapeutic activity by inhibiting cyclooxygenase and lipoxygenase pathways, suppressing prostaglandin and leukotriene synthesis, scavenging reactive oxygen species, and reducing the production of inflammatory cytokines within the colonic mucosa. However, the clinical effectiveness of Mesalamine largely depends on its ability to reach the colon in adequate concentration. Conventional oral formulations often release a considerable portion of the drug in the stomach and small intestine, resulting in reduced drug availability at the target site, decreased therapeutic efficacy, increased dosing frequency, and unnecessary systemic exposure.

Colon-targeted drug delivery systems have emerged as an effective strategy to overcome these limitations by delivering the active pharmaceutical ingredient specifically to the large intestine. Such systems protect the drug from premature release in the upper gastrointestinal tract and ensure that the majority of the dose becomes available at the site of inflammation. Site-specific delivery not only enhances therapeutic efficacy but also minimizes systemic adverse effects, reduces dose requirements, and improves patient compliance. Colon-targeted formulations are particularly advantageous for drugs intended for the treatment of ulcerative colitis, Crohn's disease, colorectal cancer, irritable bowel syndrome, and other localized colonic disorders.

Various approaches have been explored for colon-specific drug delivery, including pH-dependent systems, time-dependent formulations, pressure-controlled devices, enzyme-triggered systems, prodrug approaches, osmotic systems, multiparticulate dosage forms, and polysaccharide-based matrix tablets. Among these strategies, matrix tablets prepared using natural polysaccharides have attracted considerable attention because of their simplicity, cost-effectiveness, biocompatibility, biodegradability, and excellent safety profile. Natural polymers remain relatively stable during passage through the stomach and small intestine but undergo enzymatic degradation by the colonic microflora, thereby facilitating controlled drug release specifically in the colon.

Xanthan gum and guar gum are among the most widely investigated natural polymers for controlled and colon-targeted drug delivery applications. Xanthan gum is a high-molecular-weight extracellular polysaccharide possessing excellent swelling, gel-forming, and viscosity-enhancing properties that enable sustained drug release. Guar gum is a naturally occurring galactomannan polysaccharide that undergoes degradation by colonic bacterial enzymes while exhibiting minimal degradation in the upper gastrointestinal tract. The combination of these polymers produces a robust hydrophilic matrix capable of regulating water uptake, maintaining tablet integrity, controlling matrix erosion, and providing prolonged release of the incorporated drug within the colonic environment.

Optimization of pharmaceutical formulations is essential for achieving the desired balance between swelling characteristics, matrix integrity, mechanical strength, and drug release behavior. Conventional trial-and-error methods are laborious, time-consuming, and often fail to identify the optimum formulation with a minimal number of experiments. Statistical experimental design techniques provide a systematic approach for evaluating formulation variables and their interactions while reducing experimental workload. Among these, the 3^2 full factorial design is widely employed to investigate the effects of two independent variables at three levels on multiple formulation responses. This approach facilitates mathematical modeling, optimization, and prediction of formulation performance with greater accuracy and reproducibility.

In the present study, colon-targeted Mesalamine matrix tablets were developed using Xanthan gum and Guar gum as natural matrix-forming polymers. A 3^2 full factorial design was employed to optimize polymer concentrations and evaluate their influence on swelling behavior and in vitro drug release characteristics. The developed formulations were subjected to comprehensive preformulation studies,

drug-excipient compatibility analysis by Fourier Transform Infrared (FTIR) spectroscopy, pre- and post-compression evaluation, swelling studies, in vitro dissolution testing under simulated gastrointestinal conditions, statistical optimization using analysis of variance (ANOVA), and accelerated stability studies. The overall objective of the investigation was to develop a stable, reproducible, and effective colon-targeted oral drug delivery system capable of minimizing premature drug release in the upper gastrointestinal tract while providing sustained and site-specific delivery of Mesalamine to the colon for improved management of inflammatory bowel diseases.

MATERIALS AND METHODS:

MATERIALS:

Mesalamine was obtained as a gift sample from Wockhardt Pharmaceutical Ltd., Aurangabad, India. Xanthan gum was procured from Genuine Chemical Company, Mumbai, India, while guar gum, starch, sodium starch glycolate, and talc were purchased from Research Lab Fine Chemical Industries, Mumbai, India. Lactose and magnesium stearate were supplied by Ozone International, Mumbai, India. All chemicals and excipients used in the formulation were of analytical reagent (AR) or laboratory reagent (LR) grade and were used as received without further purification. Distilled water and other routine laboratory reagents employed during the study were of analytical grade.

METHODOLOGY:

Preformulation Studies

Preformulation studies were performed to evaluate the physicochemical properties of mesalamine and its compatibility with selected excipients. The investigated parameters included physical appearance, solubility, melting point, partition coefficient, UV analysis, calibration curve, and FTIR compatibility studies to support the development of a colon-targeted tablet.

Physical Characterization

Mesalamine was examined visually and under a compound microscope to determine its appearance, color, and physical nature.

Solubility Study

The solubility of mesalamine was determined in distilled water, 0.1 N HCl, and phosphate buffer (pH 6.8). Excess drug was shaken with each medium for 24 h, filtered, and analyzed using a UV–Visible spectrophotometer. The study was performed in triplicate.

Melting Point

The melting point of mesalamine was determined by the capillary tube method, and the average of three readings was recorded.

Partition Coefficient

The partition coefficient was determined using the n-octanol/water system. The concentration of drug in the aqueous phase was measured by UV spectrophotometry, and the experiment was conducted in triplicate.

UV Spectral Analysis and Calibration Curve

The λmax of mesalamine was determined by scanning a 10 µg/mL solution in phosphate buffer (pH 6.8) over the range of 200–400 nm using a UV–Visible spectrophotometer. A standard calibration curve was prepared using serial dilutions of 10–100 µg/mL, and absorbance was measured at the selected λmax.

Drug–Excipient Compatibility Study

Drug–excipient compatibility was evaluated using Fourier Transform Infrared (FTIR) spectroscopy. The spectra of pure mesalamine and its physical mixtures with excipients were recorded over the range of 4000–400 cm^{-1} using the KBr pellet method and compared for possible interactions.

Experimental Design

A 3^2 full factorial design (FFD) was employed to optimize the colon-targeted mesalamine matrix tablets. The concentrations of xanthan gum (X_1) and guar gum (X_2) were selected as independent variables at three levels (-1, 0, +1), while all other formulation variables were kept constant. A total of nine experimental formulations (F1–F9) were prepared according to the factorial design to evaluate the effect of polymer concentration on tablet performance.

Preparation of Mesalamine Matrix Tablets

Mesalamine matrix tablets were prepared by the wet granulation method. Mesalamine, xanthan gum, guar gum, lactose, and sodium starch glycolate were passed through #150 sieve and blended uniformly. The powder mixture was granulated using 10% w/v starch paste as a binder, passed through #12 sieve, and dried at 50°C until the moisture content reached 1–1.2%. The dried granules were resized through #22 sieve, lubricated with magnesium stearate and talc (1:2, w/w), and compressed using a 13 mm flat punch at a compression pressure of approximately 5.3 kg/cm^2. Nine formulations (F1–F9) containing varying concentrations of xanthan gum and guar gum were prepared according to the factorial design, with a target tablet weight of 700 mg (F1–F8), while formulation F9 was adjusted to 750 mg to accommodate the highest polymer content.

Table 1: Formulation of Mesalamine matrix tablet in 3^2 factorial design

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Mesalamine	300	300	300	300	300	300	300	300	300
Xanthun gum	105	140	175	105	140	175	105	140	175
Guar gum	105	105	105	140	140	140	175	175	175
Sodium Starch Glycolate (4 %)	28	28	28	28	28	28	28	28	28
Starch (10 %)	35	35	35	35	35	35	35	35	35
Mg. Stearate & Talc 1:2 (2%w/w)	14	14	14	14	14	14	14	14	14
Lactose	113	78	43	78	43	8	43	8	23
Total (mg)	700	700	700	700	700	700	700	700	750

Evaluation of Powder Blend (Pre-compression Studies)

The prepared granules were evaluated for their flow and compression characteristics by determining bulk density, tapped density, Carr's compressibility index, Hausner's ratio, and angle of repose using standard pharmacopoeial procedures. These parameters were assessed to determine the suitability of the granules for tablet compression.

Evaluation of Matrix Tablets (Post-compression Studies)

The compressed tablets were evaluated for appearance, thickness, diameter, hardness, friability, weight variation, and drug content uniformity using standard analytical methods. All tests were performed in triplicate, and the results were expressed as mean ± standard deviation.

***In Vitro* Drug Release Study**

The dissolution study was carried out using the USP Apparatus I (basket method) at 50 rpm and 37 ± 0.5°C. Tablets were initially tested in 0.1 N HCl (pH 1.2) for 2 h, followed by phosphate buffer (pH 7.4) for 3 h to simulate gastrointestinal transit. Subsequently, drug release was evaluated in phosphate buffer (pH 6.8) to mimic colonic conditions. Samples were withdrawn at predetermined intervals, replaced with fresh dissolution medium, and analyzed spectrophotometrically at 331 nm.

Swelling Study

The swelling behavior of the matrix tablets was evaluated in phosphate buffer (pH 6.8) at 37 ± 0.5°C. Tablets were removed at predetermined intervals, gently blotted to remove excess surface moisture, and weighed. The swelling index (%) was calculated from the percentage increase in tablet weight. All experiments were performed in triplicate.

Statistical Analysis

Experimental data were expressed as mean ± standard deviation (SD). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by regression analysis, with $p < 0.05$ considered statistically significant.

Stability Study

The optimized formulation was subjected to accelerated stability testing according to ICH guidelines at 40 ± 2°C/75 ± 5% RH for 6 months. Samples were withdrawn at predetermined intervals and evaluated for physical appearance, drug content, and in vitro dissolution profile to assess formulation stability.

RESULTS AND DISCUSSION:

Preformulation Studies

The preformulation studies confirmed the suitability of mesalamine for the development of a colon-targeted matrix tablet. The drug exhibited characteristic physical properties, an appropriate melting point, favorable solubility in physiological media, and moderate lipophilicity, supporting its application in controlled colonic drug delivery.

Table 2: Preformulation Characteristics of Mesalamine

Parameter	Observation
Appearance	White crystalline, odorless powder
Melting point (°C)	281 ± 0.5
Solubility in 0.1 N HCl (mg/mL)	9.97
Solubility in Phosphate buffer (pH 6.8) (mg/mL)	7.63
Solubility in Phosphate buffer (pH 7.4) (mg/mL)	5.84
Solubility in Distilled water (mg/mL)	0.78
Partition coefficient (Ko/w)	1.61

The observed melting point was consistent with the reported value, confirming the purity of mesalamine. The drug showed maximum solubility in 0.1 N HCl and minimum solubility in distilled water. The partition coefficient (1.61) indicated moderate lipophilicity, suggesting that mesalamine possesses suitable physicochemical characteristics for the formulation of a colon-targeted controlled-release matrix tablet.

UV Spectral Analysis and Calibration Curve

The UV spectrum of mesalamine in phosphate buffer (pH 6.8) exhibited a maximum absorbance

(λ_{max}) at 331 nm, which was consistent with the reported literature value. The calibration curve constructed over the concentration range of 10–100 µg/mL showed excellent linearity with a regression equation of y = 0.0193x + 0.0132 and a correlation coefficient (R^2 = 0.9993), demonstrating the accuracy and reliability of the developed analytical method for quantitative estimation of mesalamine.

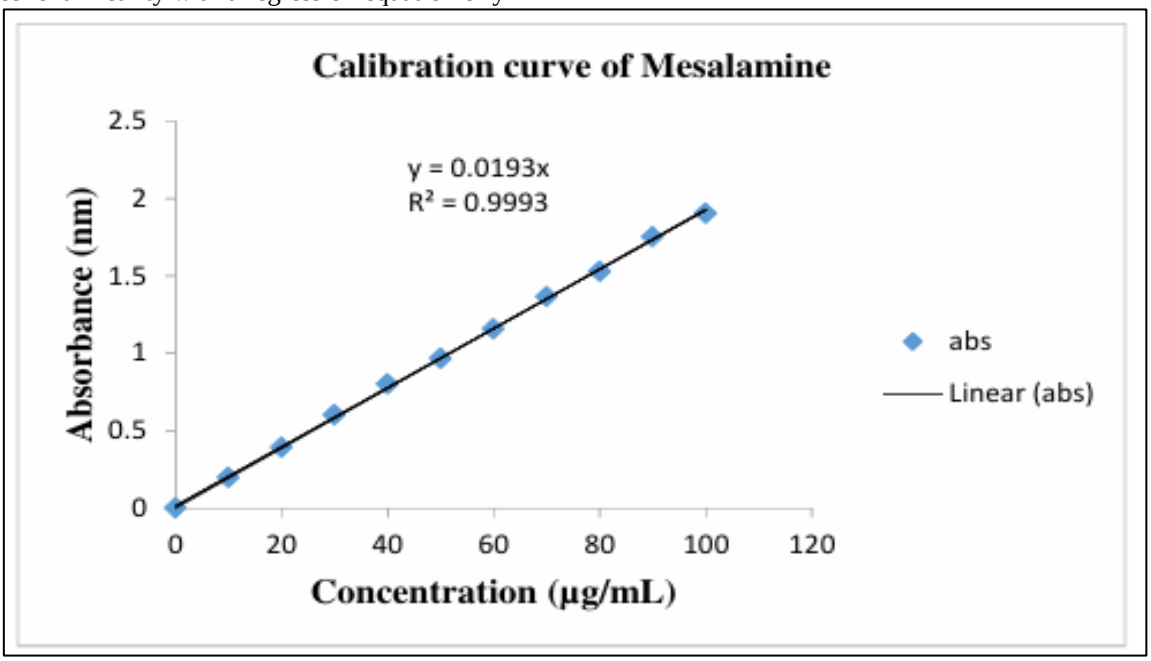

Fig. 1: Standard calibration curve of Mesalamine in PBS pH 6.8

Drug–Excipient Compatibility Study

The FTIR spectra of pure mesalamine, individual excipients, and the optimized formulation were analyzed to evaluate drug–excipient compatibility. Mesalamine exhibited characteristic absorption peaks at 3400 cm^{-1} (N–H stretching), 3010 cm^{-1} (C–H stretching), 1642.37 cm^{-1} (C=O stretching), and 1442.88 cm^{-1} (C=C stretching). These characteristic peaks were retained in the optimized formulation without significant shifts or disappearance, indicating the absence of any chemical interaction between mesalamine and the selected polymers.

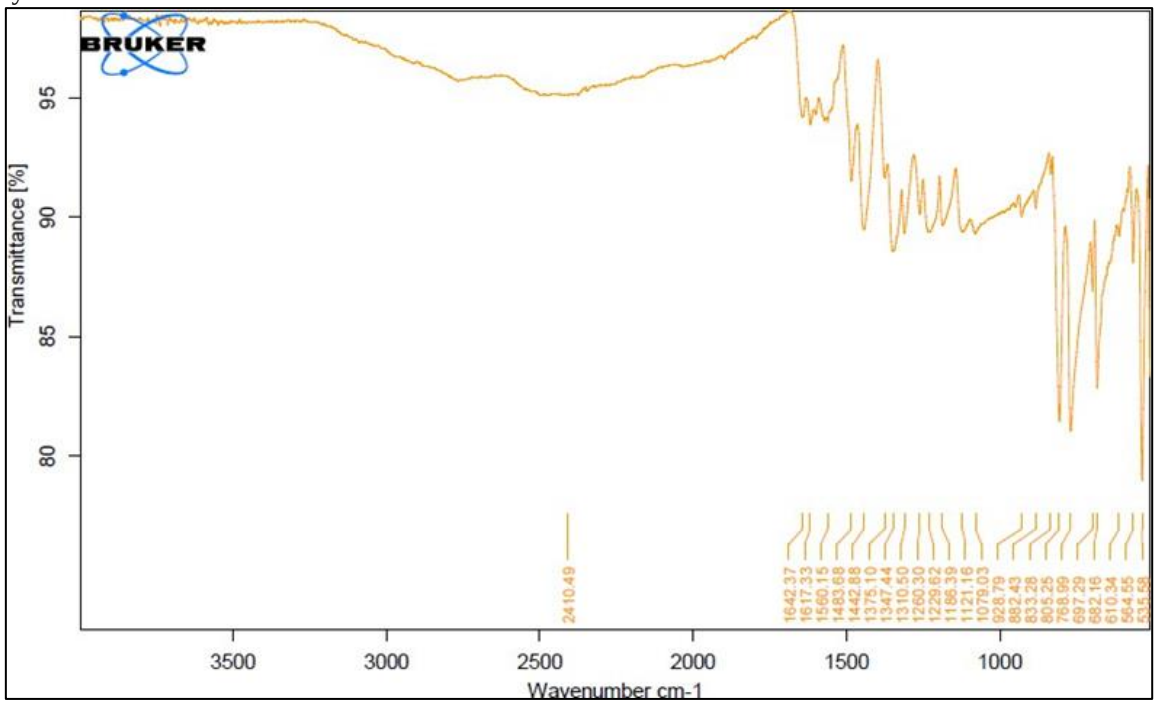

Fig. 2: FTIR Spectra of Mesalamine

Formulation Development and Pre-compression Evaluation

A total of nine mesalamine matrix tablet formulations (F1–F9) were prepared using a 3^2 full factorial design by varying the concentrations of xanthan gum and guar gum. Formulations F1–F8 had a tablet weight of 700 mg, whereas F9 was adjusted to 750 mg.

The powder blends of all formulations exhibited satisfactory flow and compression characteristics. The angle of repose ranged from 17.29° to 23.84°, indicating good flowability. Bulk density and tapped density varied from 0.57–0.64 g/mL and 0.66–0.75 g/mL, respectively. The Carr's compressibility index (13.51–15.88%) and Hausner's ratio (1.15–1.22) were within acceptable limits, confirming good flow properties and compressibility suitable for tablet compression.

Table 3: Pre-compression Evaluation of Powder Blends (n = 3)

Parameter	Range Obtained	Interpretation
Angle of repose (°)	17.29–23.84	Excellent to good flow
Bulk density (g/mL)	0.57–0.64	Acceptable
Tapped density (g/mL)	0.66–0.75	Acceptable
Carr's compressibility index (%)	13.51–15.88	Good compressibility
Hausner's ratio	1.15–1.22	Free-flowing powder

The pre-compression evaluation demonstrated that all powder blends possessed satisfactory flowability and compressibility, indicating their suitability for the preparation of mesalamine matrix tablets by the wet granulation method.

Post-compression Evaluation of Mesalamine Matrix Tablets

All formulations (F1–F9) were evaluated for post-compression quality attributes. The tablet thickness ranged from 4.00–4.21 mm, while the diameter varied between 13.05 and 13.15 mm, indicating uniform tablet dimensions. The hardness values (5.23–6.20 kg/cm²) demonstrated adequate mechanical strength, and friability remained below 1% (0.31–0.47%), confirming good resistance to abrasion. The average tablet weight was within pharmacopoeial limits (699.60–750.40 mg), and drug content ranged from 96.10–99.75%, indicating satisfactory content uniformity among all formulations.

Table 4: Post-compression Evaluation of Mesalamine Matrix Tablets (n = 3)

Parameter	Range Obtained	Interpretation
Thickness (mm)	4.00–4.21	Uniform
Diameter (mm)	13.05–13.15	Uniform
Hardness (kg/cm²)	5.23–6.20	Good mechanical strength
Friability (%)	0.31–0.47	Within IP limit (<1%)
Average tablet weight (mg)	699.60–750.40	Within acceptable limit
Drug content (%)	96.10–99.75	Uniform drug distribution

The post-compression evaluation demonstrated that all formulations complied with pharmacopoeial specifications. The tablets exhibited uniform dimensions, adequate hardness, low friability, acceptable weight variation, and satisfactory drug content, confirming the suitability of the wet granulation process for the preparation of colon-targeted mesalamine matrix tablets.

Swelling Index Study

The swelling behavior of mesalamine matrix tablets was evaluated in phosphate buffer (pH 6.8) for 6 h. All formulations exhibited a gradual increase in swelling with time due to progressive hydration of xanthan gum and guar gum. The swelling index increased with increasing polymer concentration, while the tablets maintained their structural integrity throughout the study. After 6 h, the swelling index ranged from 59.28% to 69.42%, with the order of swelling observed as F9 > F8 > F7 > F6 > F5 > F4 > F3 > F2 > F1.

Table 5: Swelling Index of Mesalamine Matrix Tablets (n = 3)

Parameter	Observation
Swelling medium	Phosphate buffer (pH 6.8)
Study duration	6 h
Initial swelling index (%)	15.71–23.86
Final swelling index after 6 h (%)	59.28–69.42
Highest swelling formulation	F9 (69.42%)
Lowest swelling formulation	F1 (59.28%)
Swelling order	F9 > F8 > F7 > F6 > F5 > F4 > F3 > F2 > F1

The swelling index increased progressively with increasing concentrations of xanthan gum and guar gum, demonstrating the hydrophilic nature of the polymers. Greater polymer content enhanced water uptake and gel formation, which is expected to contribute to sustained and colon-targeted drug release.

***In Vitro* Drug Release Study**

The in vitro drug release study demonstrated that all formulations successfully minimized drug release in the

stomach (pH 1.2) and small intestine while achieving maximum release in the colonic medium (pH 6.8). Drug release in the gastric medium was limited to 3.53–5.90% during the first 2 h, followed by 29.82–37.13% release in the intestinal medium over the next 3 h. The remaining 62.52–69.53% of mesalamine was released in the colonic medium within 12 h, confirming the effectiveness of the xanthan gum and guar gum matrix in providing colon-specific sustained drug delivery.

Table 6: *In Vitro* Drug Release Profile of Mesalamine Matrix Tablets

Formulation	Drug Release in Stomach (2 h) (%)	Drug Release in Small Intestine (5 h) (%)	Drug Release in Colon (12 h) (%)	Total Drug Release at 12 h (%)
F1	3.53	33.81	65.00	99.62
F2	4.62	33.11	66.83	99.94
F3	3.67	29.82	69.53	99.35
F4	5.90	32.51	64.73	100.24
F5	5.41	31.97	67.25	99.22
F6	4.09	36.11	63.80	99.91
F7	3.98	33.04	65.38	98.42
F8	4.35	35.55	63.46	99.01
F9	4.69	37.13	62.52	99.65

All formulations exhibited the desired colon-targeted release pattern by restricting mesalamine release in the upper gastrointestinal tract and delivering the majority of the drug in the colonic environment. Among the formulations, F3 showed the highest colonic drug release (69.53%) with minimal gastric release (3.67%), indicating the most efficient colon-targeting performance. Overall, the combination of xanthan gum and guar gum effectively controlled drug release and maintained tablet integrity throughout the dissolution study, making the developed matrix tablets suitable for colon-targeted delivery of mesalamine.

Stability Study

The optimized formulation (F3) was subjected to accelerated stability testing at 40 ± 2°C/75 ± 5% RH for 6 months. The formulation was periodically evaluated for its in vitro drug release profile. No significant changes ($p > 0.05$) were observed in the dissolution behavior throughout the study, indicating that the optimized formulation remained physically and chemically stable under accelerated storage conditions. These findings suggest that the formulation is expected to remain stable for at least 2 years under normal storage conditions.

Table 7: Accelerated Stability Study of Optimized Formulation (F3)

Parameter	Initial	After 180 Days (40°C/75% RH)	Observation
Drug release at 2 h (%)	3.67	5.33	No significant change
Drug release at 5 h (%)	33.49	34.25	Comparable release profile
Drug release at 12 h (%)	99.35	100.23	Maintained complete drug release
Physical appearance	Uniform	Uniform	No visible change
Stability	Stable	Stable	Suitable for long-term storage

The optimized formulation (F3) retained its dissolution characteristics after 180 days of accelerated storage, with only minor variations in drug release that were within acceptable limits. The formulation showed no evidence of physical instability or significant alteration in release behavior, confirming the effectiveness of the xanthan gum–guar gum matrix system. The stability results indicate that F3 possesses adequate shelf stability and is suitable for long-term storage under recommended conditions.

CONCLUSION:

The present investigation successfully developed and optimized a colon-targeted matrix tablet of Mesalamine using Xanthan gum and Guar gum as natural biodegradable matrix-forming polymers. The application of a 3^2 full factorial design enabled systematic optimization of the formulation variables and established their significant influence on swelling behavior and drug release characteristics. Preformulation and compatibility studies confirmed the suitability of Mesalamine and the selected excipients for formulation development. All prepared formulations demonstrated satisfactory flow properties, compressibility, mechanical strength, uniform drug content, and compliance with pharmacopoeial quality standards. The optimized formulation (F3) exhibited controlled swelling, excellent matrix integrity, minimal drug release in simulated gastric and intestinal media, and maximum sustained drug release in simulated colonic conditions, thereby achieving effective colon-specific drug delivery. Accelerated stability studies confirmed that the optimized formulation remained physically and chemically stable without significant changes in its dissolution profile throughout the study period.

Overall, the developed colon-targeted Mesalamine matrix tablet provides a promising oral drug delivery platform capable of enhancing local drug

availability in the colon, reducing systemic adverse effects, and improving therapeutic efficacy for the treatment of ulcerative colitis and other inflammatory bowel diseases. These findings support the potential of the optimized formulation for further preclinical evaluation, in vivo pharmacokinetic studies, and clinical investigations toward the development of an effective colon-specific pharmaceutical product.

CONFLICT OF INTREST:

The author declares that there is no conflict of interest.

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