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THERAPEUTIC POTENTIAL OF MESALAMINE-PROBIOTIC COMBINATION IN ENTERIC-COATED TABLET FOR MODULATING GUT INFLAMMATION IN IBD

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ABSTRACT
Background: Mesalamine is widely used for inflammatory bowel disease (IBD) due to its local anti-inflammatory action, while probiotics help restore intestinal microbiota and modulate immune responses. Combining both may offer synergistic benefits for IBD management. This study aimed to develop and evaluate colon-targeted enteric-coated tablets containing a mesalamine-probiotic combination. **Methodology:** Core tablets containing mesalamine, selected probiotics, and polymers were prepared by dry granulation. Pre- and post-compression parameters were evaluated. The optimized batch was coated with Eudragit® S100 (2–5%) to achieve pH-dependent release. In vitro dissolution and probiotic viability in simulated gastric conditions were assessed. **Result and Discussion:** The optimized formulation showed acceptable physical properties and negligible drug release in gastric pH, followed by targeted colonic release exceeding 90% at intestinal/colonic pH. Mesalamine release followed Higuchi kinetics, suggesting diffusion-controlled behavior. Swelling studies demonstrated gradual polymer hydration and matrix erosion. Probiotic viability studies demonstrated strain-dependent survival: Saccharomyces boulardii and Streptococcus thermophilus retained>90% viability after 150 min of simulated gastric exposure, whereas *Lactobacillus acidophilus* and *Bifidobacterium bifidum* exhibited approximately 1.2–1.3 log reductions, indicating greater acid sensitivity. The combination of enteric coating enabled efficient colon targeting and sustained release. Differential strain viability emphasized the importance of selecting acid-resistant probiotics or employing protective delivery systems. **Conclusion:** The developed mesalamine–probiotic enteric-coated tablets demonstrated colon-specific drug release and strain-dependent probiotic survival in vitro, indicating their potential as a candidate formulation requiring further optimization, particularly for acid-sensitive bacterial strains.

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INTRODUCTION

Inflammatory bowel disease (IBD), comprising ulcerative colitis and Crohn's disease, is a persistent inflammatory disorder of the gastrointestinal tract marked by alternating episodes of remission and relapse. Its global incidence continues to rise, posing significant clinical and socio-economic challenges. Current evidence increasingly links IBD pathogenesis to aberrant immune responses, epithelial barrier dysfunction, and alterations in gut microbiota [1-3]. Mesalamine (5-aminosalicylic acid) is widely used in mild-to-moderate IBD for its local anti-inflammatory activity, primarily through inhibition of the cyclooxygenase and lipoxygenase pathways [4]. However, its therapeutic efficacy depends strongly on the formulation's ability to deliver the drug intact to the colon, where inflammation is typically localized [4, 5]. Probiotics-live beneficial microorganisms-have gained considerable attention as adjuncts in IBD management due to their ability to modulate intestinal immunity, enhance barrier function, and correct dysbiosis [6, 7]. Strains such as *Bifidobacterium*, *Lactobacillus*, *Streptococcus thermophilus*, and *Saccharomyces boulardii* have shown promising roles in maintaining gut homeostasis [6]. Combining mesalamine with probiotics in a single dosage form may provide dual benefits: anti-inflammatory action and restoration of the microbiota. For such a combination to be effective, it is critical that both components reach the colon unaltered. Enteric coating with pH-responsive polymers (e.g., Eudragit® S100) is a well-established strategy for targeted release at intestinal/colonic pH [8]. This study focuses on the formulation and evaluation of enteric-coated tablets containing mesalamine and selected probiotics to achieve colon-specific delivery, sustained release, and enhanced probiotic viability.

MATERIAL AND METHODS

Mesalamine and pharmaceutical excipients (MCC, PVP K-30, magnesium stearate, and talc) were procured from certified suppliers. Probiotic strains—*Saccharomyces boulardii SKB BSB-24, Bifidobacterium bifidum SK B06, Lactobacillus acidophilus SKB-14,* and *Streptococcus thermophilus*-were obtained from SK Bio BIZ, Nashik. Eudragit® S100 was used as the enteric polymer. All solvents and chemicals were analytical grade.

PREFORMULATION STUDIES

Quantification of Mesalamine by UV Spectroscopy

Mesalamine solutions were prepared in 0.01 N HCl, phosphate buffer pH 6.8, and pH 7.4. Samples were scanned from 200 to 400 nm to determine λmax, followed by the construction of calibration curves over 10-50 µg/mL [9].

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra of mesalamine, excipients, and their mixtures were recorded using ATR-IR to evaluate potential interactions based on characteristic peak shifts.

Differential Scanning Calorimetry (DSC)

Approximately 5 mg of mesalamine was placed in aluminum pans and heated from 25 to 300°C at 10°C/min to assess thermal behavior and compatibility.

Preparation of Mesalamine Core Tablets

All ingredients were accurately weighed and passed through a #60 mesh sieve. The drug was initially blended with a diluent, then gently mixed with probiotics and other excipients to ensure uniform distribution. Lubricant and glidant were added and mixed briefly. The final blend was directly compressed into tablets using a single-punch tablet compression machine. Eight formulations (F1–F8) were prepared at varying ratios, as mentioned in Table 1.

Enteric Coating of Core Tablets

Enteric coating of the compressed core tablets was performed using a 5% w/v Eudragit® S100 solution prepared in isopropyl alcohol. Tablets were coated using multiple dipping cycles, with intermediate drying at room temperature after each cycle. To assess coating uniformity and justify the precision of the manual dipping method, the weight gain of ten tablets after coating was measured individually. The % weight gain and its variation were calculated to evaluate coating thickness uniformity [8].

EVALUATION PARAMETERS

Flow Properties

Angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio were assessed to evaluate granule flowability.

Physicochemical Evaluation of Tablets

Weight variation, hardness, friability, thickness, and drug content were tested using standard pharmacopeial procedures.

Coating Uniformity Data

The enteric-coated tablets exhibited a mean percentage weight gain of 5.04 ± 0.05%, indicating minimal inter-tablet variation. The low standard deviation (<1%) confirms that the multiple-dipping technique yielded a uniform coating thickness, thereby

supporting the reproducibility of the manual coating method at the laboratory scale.

Dissolution Studies

Using the USP Type II apparatus, tablets were sequentially tested in 0.1 N HCl (pH 1.2) for 2 hours, in phosphate buffer (pH 6.8) for 3 hours, and in phosphate buffer (pH 7.4) thereafter. Samples were analyzed at appropriate wavelengths, and cumulative release profiles were plotted.

Probiotic Viability

Viable counts were determined using the pour plate method on MRS and YPD agar. Samples were diluted and incubated under appropriate conditions, and colony-forming units (CFU/mL) were calculated.

Drug Release Kinetics

Release data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to determine release mechanisms.

Statistical Analysis

All experimental data are expressed as mean ± standard deviation (SD), with experiments performed in triplicate (n = 3). Statistical analysis was carried out using one-way analysis of variance (ANOVA) to compare differences among formulations and probiotic strains. Where applicable, Tukey's post hoc test was employed to identify pairwise differences. A value of $p < 0.05$ was considered statistically significant.

RESULT AND DISCUSSION

Pre-Formulation Studies

Mesalamine exhibited a λmax at 330 nm (pH 7.4) with excellent linearity ($R^2 = 0.998$), as shown in Figures 1 and 2. FTIR (Table 2) and DSC revealed no significant interaction between the drug and excipients.

FT-IR analysis

FTIR analysis confirmed the presence of characteristic functional groups of mesalamine as shown in Table 2, indicating no significant interaction between the drug and excipients.

Table 1: Composition of the matrix tablet of mesalamine and the tablet

S. No.	Ingredients	Quantity							
		F1	F2	F3	F4	F5	F6	F7	F8
1.	Mesalamine (mg)	400	400	400	400	400	400	400	400
2.	Probiotics (mg)	250	250	250	250	250	250	250	250
3	Magnesium stearate (mg)	8	8	8	8	8	8	8	8
4.	Talc (mg)	10	10	10	10	10	10	10	10
5.	MCC (mg)	170	170	120	120	120	170	170	120
6.	PVP K 30 (% W/W)	5	5	2	2	5	2	2	5
7.	Eudragit S 100 (% w/w)	2	5	2	5	2	5	2	5

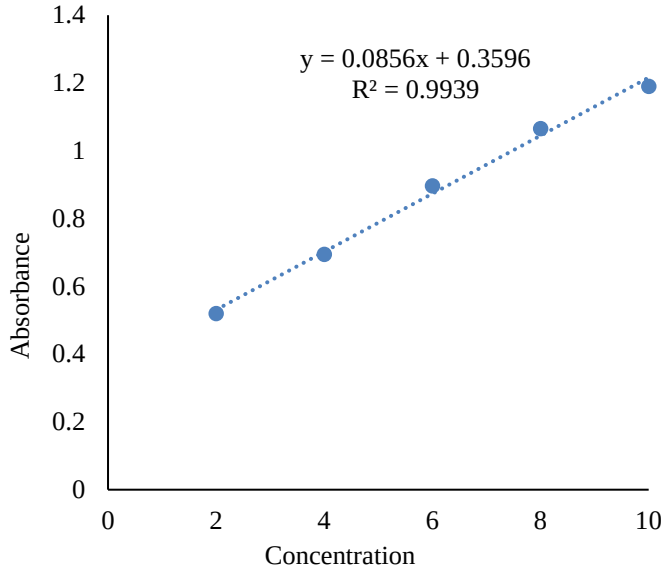

Figure 1: Calibration curve in 0.1 N HCl

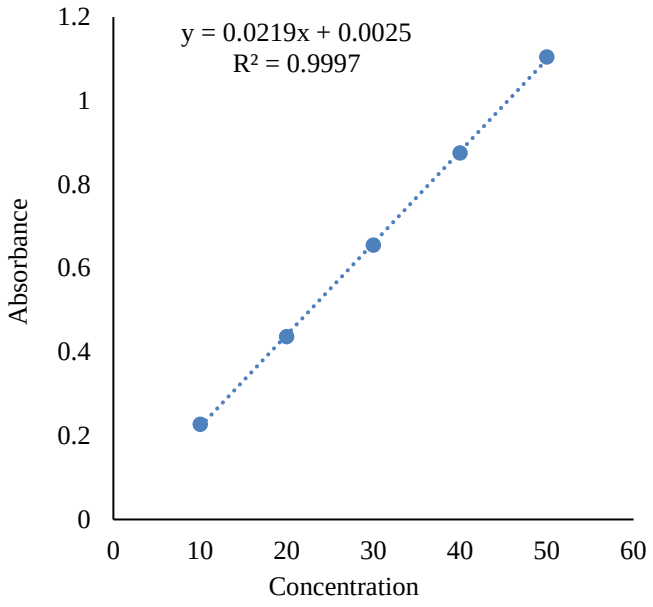

Figure 2: Calibration curve in Phosphate buffer.

Table 2: Functional groups identified in the IR of mesalamine

Functional group	Standard range (cm^{-1})	Observed range (cm^{-1})
-OH (hydroxyl)	3200-3600	3435.3
C-H (aliphatic stretch)	2800-3000	2778.96, 2521.53
C=O (carbonyl)	1640-1700	1652, 1624.1
N-H (amine stretch)	3300-3500	3435.3
C-N (aromatic amine)	1180-1360	1354.9, 1350.52
C=C (aromatic ring)	1450-1600	1573.86, 1600.46
C-O (phenol/Ether)	1000-1300	1371.7, 1181.93, 1086.77

DSC analysis: The DSC thermogram showed a sharp endothermic peak, confirming the crystalline nature of mesalamine (figure 3).

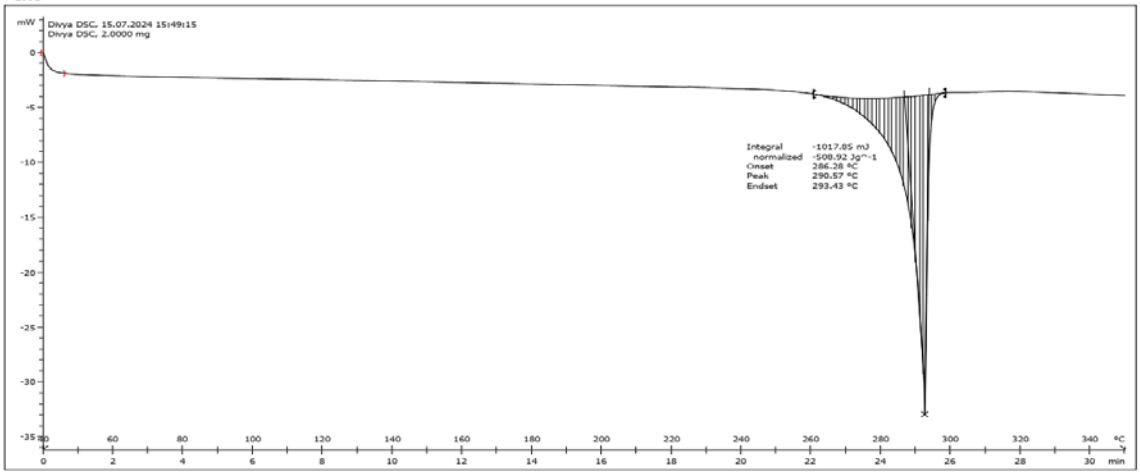

Figure 3: DSC thermogram of mesalamine

Table 3: Micromeritic properties of mesalamine and probiotic granules (mean ± SD, n = 3)

Batch	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Carr's index (%)	Angle of repose (°)
B1	0.46 ± 0.3	0.50 ± 0.6	1.11 ± 0.6	9.25 ± 0.5	28.7 ± 0.4
B2	0.44 ± 0.4	0.49 ± 0.6	1.10 ± 0.3	9.45 ± 0.4	26.3 ± 0.2
B3	0.43 ± 0.3	0.50 ± 0.5	1.15 ± 0.5	13.1 ± 0.2	29.5 ± 0.5
B4	0.47 ± 0.2	0.51 ± 0.3	1.09 ± 0.2	9.12 ± 0.3	27.4 ± 0.4
B5	0.42 ± 0.6	0.50 ± 0.7	1.18 ± 0.2	15.20 ± 0.3	27.1 ± 0.2
B6	0.46 ± 0.4	0.50 ± 0.2	1.10 ± 0.4	9.00 ± 0.6	28.0 ± 0.5
B7	0.44 ± 0.6	0.48 ± 0.5	1.13 ± 0.7	11.35 ± 0.4	26.7 ± 0.3
B8	0.43 ± 0.5	0.50 ± 0.3	1.16 ± 0.6	13.3 ± 0.2	30.2 ± 0.3

Granule Properties

Values of angle of repose (26–30°), Carr's index (9–15%), and Hausner ratio (1.08–1.18) indicated satisfactory flow and compressibility across all batches as summarized in Table 3.

Tablet Evaluation

All batches complied with pharmacopeial limits for hardness, friability (<1%), weight variation, and thickness.

Physicochemical evaluation of the release of enteric-coated tablets

All enteric-coated tablets resisted acidic conditions, releasing less than 3% drug in 2 h. Subsequent exposure to intestinal/ colonic pH resulted in >90% release in most batches within 6–7 hours. The comparative in vitro drug release profiles of all formulations are presented in Table 5.

Table 4: Coating uniformity of enteric-coated tablets (n = 10)

Formu-lation	Core Tablet Wt. (mg)	Coating Wt. Gain (5%) (mg)	Final Tablet Wt. (mg)
F1	900	45	945
F2	900	45	945
F3	820	41	861
F4	845	42	887
F5	875	44	919
F6	900	45	945
F7	900	45	945
F8	845	42	887

Probiotic Viability

These strain-dependent differences in initial viable counts provide important insight into the challenges of formulating multi-strain probiotic combinations within a single solid dosage form. Acid resistance varied markedly:

- *S. boulardii* and *S. thermophilus* retained high viability throughout 150-min exposure.
- *L. acidophilus* and *B. bifidum* showed notable reductions, suggesting sensitivity to gastric acidity.
- *Bifidobacterium bifidum* exhibited comparatively lower viable counts (3.39 ± 0.05 log CFU mL^{-1} initially), which further declined to 2.13 ± 0.05 log CFU mL^{-1} after 150 minutes of simulated gastric exposure. This reduction indicates high acid sensitivity of *Bifidobacterium* species under gastric conditions.

Table 5: Comparative in vitro % drug release profiles of mesalamine-probiotic enteric-coated tablets

Time(Hr)	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6	Batch 7	Batch 8
0	0	0	0	0	0	0	0	0
1	2.28	0.82	3.48	2.99	1.50	2.89	1.23	2.10
2	21.48	9.33	23.48	35.43	5.13	19.4	15.10	31.79
3	65.99	29.5	49.75	61.35	25.83	38.98	68.68	44.44
4	79.83	58.2	73.53	75.98	52.77	57.33	84.64	61.27
5	92.94	78.79	90.38	87.48	91.87	89.43	90.71	75.54
6	93.67	92.35	91.28	98.32	92.45	90.24	103.45	87.83
7	93.98	93.57	92.37	99.23	92.89	91.26	104.02	99.98

Table 6: Kinetic model fitting for optimized formulation

R^2	Parameter
0.923	–
0.948	–
0.991	–
0.976	n = 0.61

Among the tested models, Higuchi kinetics exhibited the highest correlation coefficient (R^2 = 0.991), indicating diffusion-controlled drug release from the hydrophilic matrix system as summarized in Table 6.

The viability of probiotic strains during simulated gastric exposure is presented in Table 7.

Table 7: Viability of probiotic microorganisms in simulated gastric juice (log CFU mL^{-1})

Microorganism	0 min	30 min	60 min	90 min	120 min	150 min
Saccharomyces boulardii	8.21 ± 0.08	8.05 ± 0.07	7.86 ± 0.09	7.62 ± 0.06	7.41 ± 0.08	7.28 ± 0.07
Lactobacillus acidophilus	5.12 ± 0.06	5.01 ± 0.05	4.71 ± 0.07	4.42 ± 0.06	4.15 ± 0.05	3.89 ± 0.06
Bifidobacterium bifidum	3.39 ± 0.05	3.24 ± 0.04	3.05 ± 0.06	2.83 ± 0.05	2.56 ± 0.04	2.13 ± 0.05
Streptococcus thermophilus	8.32 ± 0.07	8.14 ± 0.06	7.91 ± 0.08	7.68 ± 0.06	7.49 ± 0.05	7.28 ± 0.06

The effect of wet granulation and drying on probiotic viability is summarized in Table 8.

Table 8: Probiotic viability before and after granulation

Probiotic strain	Before granulation (log CFU g^{-1})	After granulation & drying (log CFU g^{-1})	Log reduction
Saccharomyces boulardii	8.35 ± 0.06	8.10 ± 0.07	0.25
Lactobacillus acidophilus	5.42 ± 0.05	4.98 ± 0.06	0.44
Bifidobacterium bifidum	3.61 ± 0.04	3.15 ± 0.05	0.46
Strepto. thermophilus	8.51 ± 0.07	8.21 ± 0.06	0.30

Statistical significances across evaluated parameters is summarized in Table 9.

Table 9: Summary of statistical significance across evaluated parameters

Parameter	Statistical test	Significance
Probiotic viability	One-way ANOVA	$p < 0.001$
Drug release profiles	One-way ANOVA	$p < 0.05$
Granulation viability loss	One-way ANOVA	$p < 0.05$

DISCUSSION

The evaluation of pre-compression parameters is crucial for predicting the processability and final performance of solid dosage formulations. Uniform die filling, consistent tablet weight, and blend homogeneity depend largely on the flow characteristics of the powder mixture. In the present investigation, batches B1, B2, B4, and B6 demonstrated excellent to good flow behavior, characterized by Hausner's ratio values below 1.12 and Carr's index values under 10%. Such low values indicate good particle packing and minimal

interparticulate friction, making these batches highly suitable for direct compression. These findings suggest that the excipient composition in these batches ensured adequate relationships between bulk and tapped density, minimizing the need for additional flow enhancers. Conversely, batches B3, B5, B7, and B8 showed comparatively higher Hausner's ratio and Carr's index values; for example, batch B5 recorded a Hausner's ratio of 1.18 and a Carr's index of 15.20%, indicating moderate flow properties. This may be attributed to particle size heterogeneity, irregular particle shape, or increased moisture retention in the blend. Such formulations may require optimization by incorporating glidants such as colloidal silicon dioxide or magnesium stearate, or by modifying the granulation process to improve flow uniformity. The flow data were further supported by angle of repose measurements, in which lower angles (26–28°) corresponded to free-flowing powders, whereas higher angles (29–30°) suggested moderate cohesiveness. Overall, all batches exhibited acceptable pre-compression characteristics, with B2 and B6 standing out as optimal formulations for further tableting studies.

In addition to particle-size effects, the relatively high probiotic loading (250 mg per tablet) may have contributed to the observed variations in flow and compressibility across certain batches. Probiotic powders are typically fine, low-density, and cohesive, which can increase interparticulate friction and adversely affect flow properties. This effect was more evident in batches B3, B5, and B7, which exhibited higher Carr's index and Hausner's ratio values. The high probiotic content likely increased the blend's cohesiveness, resulting in moderate flow behavior. These observations indicate that probiotic loading is a critical formulation variable influencing micromeritic properties and should be carefully optimized in future formulations. Drug release profiles of the formulated batches revealed clear formulation-dependent variations, reflecting the influence of factors such as granule size, polymer concentration, and drug–polymer ratio. Batches 4 and 7 showed rapid, nearly complete drug release (>99% within 7 h), which can be attributed to a lower polymer content or to the presence of more hydrophilic excipients, which facilitated faster disintegration and dissolution. These batches are therefore appropriate for immediate or fast-acting drug delivery applications, where prompt therapeutic action is desired. In contrast, Batches 1 and 3 displayed a more controlled release pattern, exceeding 90% release within 6 h, suggesting sustained-release potential.

Among all formulations, Batch 2 exhibited the slowest release rate (93.57% at 7 h), indicative of an extended-release profile. Hence, Batch 2 could be considered suitable for once-daily formulations, potentially improving patient compliance. Interestingly, Batch 5 demonstrated biphasic release behavior-an initial lag phase followed by rapid release-suggesting possible polymer relaxation and subsequent burst effect. Such behavior is often desirable in colon-targeted systems, where an initial protection phase is followed by rapid drug liberation at the site of action. Overall, most batches exhibited a sigmoidal release pattern, reflecting a complex interplay of diffusion, polymer swelling, and erosion processes that govern the release kinetics in matrix-based systems.

The apparent discrepancy in initial viable counts among the probiotic strains is primarily due to intrinsic biological differences rather than formulation inconsistency. *Saccharomyces boulardii*, being a yeast, possesses a thicker, more robust cell wall, higher biomass yield, and greater tolerance to processing stresses, resulting in greater survivability compared to bacterial strains. In contrast, *Lactobacillus acidophilus* and *Bifidobacterium bifidum* are more sensitive to moisture, oxygen, organic solvents, and mechanical stress, leading to comparatively lower viable counts despite equal mass incorporation. The present study employed a fixed probiotic mass per tablet to assess formulation feasibility and comparative strain survivability, rather than to normalize CFU delivery across strains. These findings highlight the need for strain-specific loading or protective strategies in future optimized combination formulations. Collectively, the present study underscores the significant impact of formulation variables on powder flow, drug release, swelling characteristics, and probiotic viability. The interplay between polymer concentration governs drug release kinetics, while probiotic stability is dictated by strain-specific resistance and formulation-protection mechanisms. The findings suggest that *S. boulardii* and *S. thermophilus* possess inherent acid stability, making them promising candidates for direct inclusion in combination formulations, whereas *L. acidophilus* and *Bifidobacterium bifidum* necessitate protective delivery approaches. Overall, the study highlights the importance of a dual-optimization strategy—one that addresses both physicochemical performance (flow) and biological stability (probiotic survivability) to achieve an effective mesalamine-probiotic combination targeted to the colon. Such integrated formulation design ensures

enhanced therapeutic efficacy, improved patient compliance, and sustained modulation of gut inflammation in inflammatory bowel disease (IBD).

CONCLUSION

The present study successfully developed and evaluated enteric-coated tablets combining mesalamine with selected probiotic strains for targeted colonic delivery in inflammatory bowel disease (IBD). The formulation demonstrated minimal gastric release, >90% release at intestinal/colonic pH, Higuchi-type diffusion-controlled kinetics, and favorable swelling behavior, confirming its suitability for colon-specific delivery. Probiotic viability studies showed that *Saccharomyces boulardii* and *Streptococcus thermophilus* maintained high survival under acidic conditions, whereas *Lactobacillus acidophilus* and *Bifidobacterium bifidum* exhibited reduced stability, highlighting the strain-dependent differences in acid tolerance. These findings collectively indicate that combining mesalamine with probiotics offers a synergistic therapeutic approach that addresses both inflammation and dysbiosis in IBD. Despite these promising outcomes, this study has certain limitations. The evaluation was limited to in vitro and simulated gastric studies, and in vivo validation of therapeutic efficacy was not performed. Additionally, protective technologies such as microencapsulation were not employed for acid-sensitive strains, potentially affecting their survival under physiological conditions. In today's context, where IBD prevalence is steadily rising and patients increasingly seek therapies that combine effectiveness with microbiome support, colon-targeted combination systems such as the one developed here hold significant relevance. They offer potential advantages over monotherapy by improving mucosal healing, reducing relapse rates, and supporting long-term gut health. Future work should focus on incorporating protective strategies for sensitive probiotics and conducting comprehensive in vivo or clinical evaluations to confirm therapeutic benefits.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Pratiksha A. Thete contributed to study conception, formulation development, experimental work, data collection, data analysis, and manuscript drafting. Milind P. Wagh supervised the overall research, guided the formulation strategy, assisted in methodological refinement, and critically reviewed the manuscript for intellectual content. Vandana S. Nade supervised the microbiological evaluations, including probiotic viability studies, and contributed to data interpretation and manuscript revision. All authors reviewed and approved the final version of the manuscript prior to submission.

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