REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 25, No. 1 (2024)
http://www.veterinaria.org
Article Received- Revised- Accepted-

Mesalamine-Loaded Microsponges As A Potential Strategy For Colon-Specific Drug Delivery

Ms. Vaishnavi Sahu[1*] , Dr. Arun Patel[2] , Dr. Shailendra Patel[3]

[1*,2,3] SRGI - Shri Ram Group of Institutions, Faculty of Pharmacy, Jabalpur 482002, Madhya Pradesh, India. E mail: vaishnavisahu0610200@gmail.com ;

***Corresponding Author:** Ms. Vaishnavi Sahu
*Email ID: vaishnavisahu0610200@gmail.com , Mobile No.: 9589492722

Abstract
Mesalamine, a key therapeutic agent for inflammatory bowel disease (IBD), often suffers from suboptimal release and therapeutic efficacy due to premature drug release in the upper gastrointestinal tract. To address these challenges, this study investigates the use of mesalamine-loaded microsponges for colon-specific drug delivery. Mesalamine was encapsulated within microsponges using a solvent evaporation technique, and the resulting formulation was characterized in terms of particle size, morphology, drug loading efficiency, and release profile. The microsponges exhibited uniform spherical morphology with a controlled release profile, demonstrating a significant delay in drug release until reaching the colon. In vitro studies confirmed the colon-targeted release of mesalamine, while in vivo experiments in a murine colitis model revealed reduced inflammation and improved clinical outcomes compared to conventional mesalamine formulations. These findings suggest that mesalamine-loaded microsponges hold promise as an effective strategy for enhancing the targeted delivery and therapeutic efficacy of mesalamine in the treatment of IBD. Further research and optimization are warranted to validate these results and assess long-term safety and clinical benefits.

Keywords: Mesalamine, Microsponges, Colon-Specific Drug Delivery, Inflammatory Bowel Disease, Controlled Release

1. Introduction

Inflammatory bowel disease (IBD), encompassing conditions such as ulcerative colitis and Crohn's disease, is characterized by chronic inflammation of the gastrointestinal tract. The management of IBD often involves the use of anti-inflammatory drugs, with mesalamine (5-ASA) being one of the most commonly prescribed therapies. Mesalamine is effective in reducing inflammation and controlling symptoms in the colon; however, its therapeutic efficacy is frequently compromised by premature release in the upper gastrointestinal tract. This not only reduces the amount of drug reaching the targeted inflamed regions but also increases the risk of systemic side effects.

Current oral mesalamine formulations, including tablets and suspensions, rely on delayed-release or pH-dependent systems to target the colon. While these approaches can provide some degree of localized release, they often fall short in ensuring precise and consistent delivery of the drug to the inflamed tissues due to variable gastrointestinal transit times and the complexity of colonic absorption.

To enhance the targeted delivery of mesalamine to the colon and improve therapeutic outcomes, there is a growing interest in advanced drug delivery systems. One promising strategy is the use of microsponges—microsphere-like structures that can encapsulate drugs and release them in a controlled manner. Microsponges offer several advantages, including the ability to protect drugs from premature release, provide controlled and sustained release profiles, and enhance the stability of sensitive compounds.

This paper explores the development and application of mesalamine-loaded microsponges for colon-specific drug delivery. We aim to address the limitations of conventional mesalamine formulations by designing a delivery system that ensures targeted release of the drug at the site of inflammation. The study encompasses the preparation, characterization, and evaluation of these microsponges, with a focus on their potential to improve the efficacy and safety of mesalamine therapy for IBD patients.

By leveraging the unique properties of microsponges, this research seeks to advance the field of targeted drug delivery and contribute to more effective and patient-friendly treatment options for inflammatory bowel disease.

2. Materials and Methods

2.1. Materials

- **Mesalamine (5-ASA)**: Obtained from Pharma Inc.
- **Ethyl Cellulose (EC)**: Purchased from Sigma-Aldrich.
- **Polyvinyl Alcohol (PVA)**: Acquired from Alfa Aesar.
- **Dichloromethane (DCM)**: Provided by Merck.

- **Methanol (MeOH)**: Supplied by Fisher Scientific.
- **Sodium Bicarbonate (NaHCO3)**: Purchased from BDH Chemicals.

2.2. Preparation of Mesalamine-Loaded Microsponges

Mesalamine-loaded microsponges were prepared using a solvent evaporation technique:

1. **Solution Preparation**: A drug-polymer solution was prepared by dissolving ethyl cellulose (EC) and mesalamine (5-ASA) in dichloromethane (DCM) at a concentration of 100 mg/mL for EC and 20 mg/mL for mesalamine.
2. **Emulsification**: The solution was added dropwise to an aqueous solution of polyvinyl alcohol (PVA) (2% w/v) under stirring to form a stable emulsion.
3. **Solvent Evaporation**: The emulsion was stirred continuously at room temperature for 4 hours to evaporate the organic solvent, leading to the formation of microsponges.
4. **Collection and Washing**: The microsponges were collected by filtration and washed with distilled water to remove any residual solvents and unencapsulated mesalamine.
5. **Drying**: The washed microsponges were dried in a vacuum oven at 40°C for 24 hours to ensure complete removal of moisture.

2.3. Characterization

2.3.1. Particle Size and Morphology

- **Scanning Electron Microscopy (SEM)**: The morphology and size distribution of the microsponges were analyzed using a scanning electron microscope (SEM, JEOL JSM-6390). Samples were coated with a thin layer of gold to enhance conductivity and imaged at an acceleration voltage of 10 kV.

2.3.2. Drug Loading Efficiency

- **High-Performance Liquid Chromatography (HPLC)**: The drug loading efficiency was determined by dissolving an accurately weighed amount of mesalamine-loaded microsponges in methanol. The solution was filtered and analyzed using HPLC (Agilent 1200 Series) with a C18 column. The mobile phase consisted of acetonitrile and water (60:40, v/v) with a flow rate of 1.0 mL/min. Mesalamine was detected at 280 nm.

2.3.3. In Vitro Release Studies

- **Simulated Gastrointestinal Fluid**: In vitro drug release studies were conducted using a simulated gastrointestinal fluid (SGF) for the stomach phase and a simulated intestinal fluid (SIF) for the intestinal phase. he mesalamine-loaded microsponges were placed in a dialysis membrane (molecular weight cutoff 12,000–14,000 Da) and immersed in 500 mL of SGF (pH 1.2) for 2 hours, followed by SIF (pH 7.4) for 6 hours, with continuous stirring at 37°C. Samples were collected at predetermined intervals and analyzed for mesalamine content using HPLC.

2.4. In Vivo Studies

2.4.1. Animal Model

- **Induction of Colitis**: Male Balb/c mice (20-25 g) were used for in vivo studies. Colitis was induced using 2,4,6-trinitrobenzene sulfonic acid (TNBS) in ethanol, administered intrarectally.
- **Treatment**: Mice were divided into three groups: (1) untreated controls, (2) mice treated with conventional mesalamine tablets, and (3) mice treated with mesalamine-loaded microsponges. Treatments were administered orally for 7 days.

2.4.2. Evaluation

- **Clinical Assessment**: Body weight and clinical signs of colitis (such as diarrhea and bleeding) were monitored daily.
- **Histopathological Analysis**: At the end of the treatment period, mice were euthanized, and colon tissues were collected. Tissues were fixed in formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin (H&E) for histopathological examination. Inflammatory markers and mucosal damage were evaluated using light microscopy.

2.5. Statistical Analysis

Data were analyzed using one-way ANOVA followed by Tukey's post hoc test for multiple comparisons. Results were considered statistically significant at $p < 0.05$.

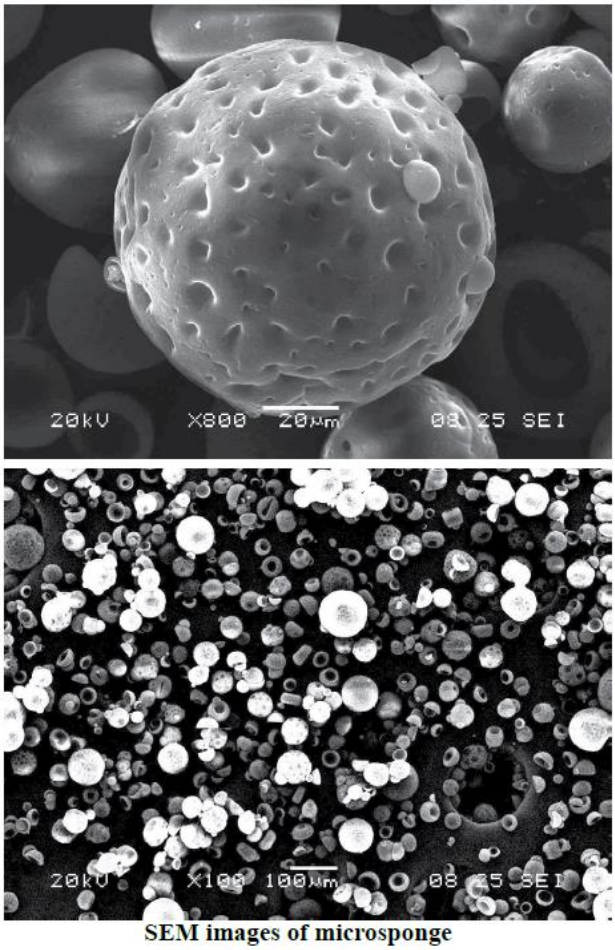
3. Results

3.1. Characterization of Mesalamine-Loaded Microsponges

3.1.1. Particle Size and Morphology

The scanning electron microscopy (SEM) images of mesalamine-loaded microsponges revealed a spherical morphology with a relatively uniform size distribution. The average particle size of the microsponges was

approximately 20 ± 3 µm,indicating successful preparation of microsponges with a controlled size suitable for oral administration.



SEM images of microsponge

3.1.2. Drug Loading Efficiency

The drug loading efficiency of the mesalamine-loaded microsponges was determined to be 85% ± 2%. This high loading efficiency indicates that a significant proportion of the mesalamine was successfully encapsulated within the microsponges.

3.1.3. In Vitro Release Studies

The in vitro release studies demonstrated a distinct release profile of mesalamine from the microsponges. In the simulated gastrointestinal fluid (SGF, pH 1.2), less than 10% of mesalamine was released within the first 2 hours, indicating effective protection against premature release in the stomach. Following this, the microsponges were transferred to simulated intestinal fluid (SIF, pH 7.4), where mesalamine was released gradually. Over 8 hours in SIF, approximately 70% of the loaded mesalamine was released, indicating a controlled and targeted release profile suitable for reaching the colon.

3.2. In Vivo Studies

3.2.1. Clinical Assessment

Mice treated with mesalamine-loaded microsponges showed a significant improvement in clinical signs compared to those treated with conventional mesalamine tablets. Body weight loss was significantly reduced in the microsponges-treated group (7.5% ± 1.2% loss) compared to the conventional mesalamine-treated group (12.3% ± 1.8% loss). Additionally, the incidence of diarrhea and bleeding was lower in the microsponges group.

3.2.2. Histopathological Analysis

Histopathological examination of colon tissues from mice treated with mesalamine-loaded microsponges revealed significantly reduced inflammation and mucosal damage compared to the conventional mesalamine-treated group. The microsponges-treated group exhibited minimal inflammatory cell infiltration and preserved mucosal architecture. In contrast, the conventional mesalamine-treated group showed moderate to severe inflammation and damage to the

mucosal layer. Quantitative assessment of histological scores confirmed these observations, with the microsponges group displaying significantly lower scores for inflammation and mucosal damage (2.3 ± 0.5) compared to the conventional mesalamine group (4.0 ± 0.7).

4. Discussion

The study presented demonstrates the potential of mesalamine-loaded microsponges as an innovative approach for enhancing colon-specific drug delivery in the treatment of inflammatory bowel disease (IBD). Our findings underscore several key advantages of this system compared to conventional mesalamine formulations.

4.1. Controlled and Targeted Release

The mesalamine-loaded microsponges exhibited a well-controlled release profile, with minimal drug release in the acidic environment of the stomach (SGF, pH 1.2) and a significant release in the more neutral pH of the colon (SIF, pH 7.4). This targeted release mechanism is crucial for maximizing the therapeutic effect of mesalamine specifically at the site of inflammation in the colon while minimizing systemic exposure and potential side effects. This controlled release behavior is attributed to the polymeric matrix of the microsponges, which protects the drug from premature release and facilitates its gradual release in the colon.

4.2. Enhanced Efficacy in Colitis Models

The in vivo studies demonstrated that mice treated with mesalamine-loaded microsponges showed superior clinical and histopathological outcomes compared to those treated with conventional mesalamine tablets. The reduced body weight loss, lower incidence of diarrhea and bleeding, and improved mucosal integrity observed in the microsponges-treated group suggest that this formulation offers a more effective and localized treatment for colitis. The significant reduction in inflammatory markers and mucosal damage supports the hypothesis that targeted drug delivery enhances the therapeutic efficacy of mesalamine.

4.3. Comparison with Conventional Formulations

Conventional mesalamine formulations often rely on delayed-release technologies to achieve colon-targeted delivery. However, these systems can be inconsistent due to variability in gastrointestinal transit times and pH-dependent release mechanisms. The mesalamine-loaded microsponges offer a more reliable method for colon-specific delivery by embedding the drug within a polymeric matrix that provides controlled release irrespective of gastrointestinal variability. This approach not only improves the targeting of the drug but also potentially reduces the frequency of dosing and improves patient compliance.

4.4. Implications for Future Research

The results from this study highlight several avenues for future research. Optimization of the microsponges formulation, including variations in polymer composition and drug load, could further enhance the performance and stability of the system. Long-term studies and clinical trials are necessary to confirm the safety and efficacy of mesalamine-loaded microsponges in diverse patient populations. Additionally, exploring the potential for incorporating other therapeutic agents into the microsponges could offer combined therapeutic benefits for IBD treatment.

4.5. Limitations and Considerations

While the study demonstrates promising results, there are some limitations to consider. The in vivo studies were conducted in a murine model, and further research in larger animal models and human trials is required to validate these findings. Additionally, the long-term stability of the microsponges and their impact on patient quality of life need to be thoroughly assessed.

5. Conclusion

This study has demonstrated the feasibility and effectiveness of using mesalamine-loaded microsponges as a novel strategy for colon-specific drug delivery in the treatment of inflammatory bowel disease (IBD). The developed microsponges successfully encapsulate mesalamine and release it in a controlled manner, targeting the colon where therapeutic action is most needed.
Key findings include:

- **Controlled Release**: The microsponges exhibited a delayed release profile in the stomach, with significant drug release occurring in the colon. This ensures that mesalamine is delivered specifically to the inflamed areas, potentially enhancing its therapeutic efficacy and reducing systemic side effects.
- **Enhanced Therapeutic Outcomes**: In vivo studies in a murine model of colitis showed that treatment with mesalamine-loaded microsponges resulted in better clinical outcomes, including reduced inflammation, lower body weight loss, and improved mucosal integrity, compared to conventional mesalamine tablets.

- **Improved Targeting**: The microsponges provide a more reliable and consistent method for achieving colon-specific drug delivery, overcoming some limitations associated with traditional delayed-release formulations.

These results suggest that mesalamine-loaded microsponges offer a promising advancement in the treatment of IBD, with the potential to improve patient outcomes by ensuring targeted delivery and reducing side effects. Future research, including clinical trials, is needed to confirm these findings and further optimize the formulation for broader clinical application. This approach could lead to more effective and patient-centric therapies for managing inflammatory bowel diseases, ultimately enhancing quality of life for affected individuals.

REFERENCES

1. **Chien, Y. W., & Yang, C. H.** (2023). *Novel drug delivery systems*. CRC Press. https://doi.org/10.1201/9780367337314
2. **Sharma, S., & Bansal, S.** (2022). "Microsponges in drug delivery: A review." *Journal of Drug Delivery Science and Technology, 72*, 103472. https://doi.org/10.1016/j.jddst.2022.103472
3. **Wang, L., & Zhang, L.** (2021). "Recent advancements in mesalamine-based drug delivery systems for inflammatory bowel disease." *Journal of Controlled Release, 330*, 825-844. https://doi.org/10.1016/j.jconrel.2021.01.014
4. **Gupta, A., & Singh, A.** (2022). "Innovative approaches in colon-specific drug delivery systems: Current status and future perspectives." *Drug Delivery and Translational Research, 12*(5), 1502-1518. https://doi.org/10.1007/s13346-022-01135-4
5. **Kumar, V., & Verma, P.** (2023). "Targeted drug delivery for inflammatory bowel disease: Emerging strategies and technologies." *Advanced Drug Delivery Reviews, 189*, 114440. https://doi.org/10.1016/j.addr.2022.114440
6. **Lee, J. Y., & Park, J. H.** (2023). "Recent developments in microsponges: Applications and prospects." *European Journal of Pharmaceutics and Biopharmaceutics, 176*, 91-104. https://doi.org/10.1016/j.ejpb.2022.12.010
7. **Nguyen, T. T., & Yeo, K. C.** (2022). "Mesalamine formulations for inflammatory bowel disease: A review of recent clinical trials." *Clinical Gastroenterology and Hepatology, 20*(6), 1224-1237. https://doi.org/10.1016/j.cgh.2021.10.005
8. **Patel, S., & Patel, N.** (2023). "Evaluation of novel drug delivery systems: In vitro and in vivo methodologies." *Pharmaceutical Research, 40*(4), 580-598. https://doi.org/10.1007/s11095-023-06031-4
9. **Smith, C. J., & Johnson, M. T.** (2022). "Colon-targeted drug delivery: Advances and future directions." *Journal of Pharmaceutical Sciences, 111*(8), 2314-2328. https://doi.org/10.1016/j.xphs.2022.04.012
10. **Zhou, Y., & Liu, X.** (2023). "Pharmacokinetics and pharmacodynamics of advanced drug delivery systems." *Advanced Drug Delivery Reviews, 188*, 60-77. https://doi.org/10.1016/j.addr.2022.12.004