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Design and Optimization of Mucoadhesive Drug Delivery System for Ulcerative Colitis

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Abstract: ***Mesalamine is the mainstay of therapy for 'ulcerative colitis (UC)', a chronic inflammatory bowel disease that suffers from poor drug localization, inconsistent release profiles, and systemic side effects. Conventional drug delivery approaches are faced with difficulty in maintaining a favorable drug retention time at the colonic site and ensuring a sustained drug release. Existing formulations suffer from the problem of insufficient polymer combinations, and variable release rates, and have not been optimized systematically. The aim of this research is to improve a mucoadhesive drug delivery system for the delivery of the anti-inflammatory agent mesalamine, for increased localized delivery, decreased side effects, and improved therapeutic efficacy. Drug excipient compatibility testing will form part of the pre-formulation studies whilst formulation development will involve the study of mucoadhesive polymers such as 'chitosan', 'carbopol', and 'pectin'. The techniques of ionic gelation and solvent evaporation will be used to encapsulate the drug. The critical formulation parameters (polymer concentration, drug load, and particle size) will be optimized using a Design of Experiments (DoE) approach, with statistical analysis by ANOVA. Mucoadhesion strength, drug release profiles, and stability in the simulated colonic fluid will be evaluated by in vitro evaluations. The expected results of this study include more consistent release of the drug, greater retention in the colon, fewer side effects, and improved patient adherence. The findings of this research will be useful in developing a more effective Mucoadhesive Drug Delivery System (MDDS) for UC treatment and may also provide useful information for designing targeted drug delivery in other gastrointestinal disorders.***

Keywords: Ulcerative colitis, mesalamine, mucoadhesive drug delivery system, polymer optimization, drug release

1. Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease which involve large colon and rectum and has persistence inflammation and ulceration. The symptoms are stomach ache, and more often passing of stools and blood in stools, tiredness, and loss of weight. Part of the first-line therapy for UC is the drug mesalamine, which is intended for the treatment of inflammation in the colon; however, this approach has pitfalls. Localized drug delivery of Mesalamine is however poor due to high drug metabolism prior to targeting the inflamed tissue, the variability in releasing the drug within the digestive system as well as the high possibilities of having systematic side effects such as; headaches, nausea, probable effects on kidneys and liver especially with long term use of the drug. Such limitations depict more significant necessity for the development of colon targeted drug delivery systems which would have better therapeutic efficacy and minimal side effects anywhere else outside the gastrointestinal tract (Chibbar *et al*., 2020). A solution is provided by mucoadhesive drug delivery systems (MDDS), which provide sustained release and improve drug retention at the colonic site (Kumar *et al*., 2022). These systems rely on mucoadhesive polymers, such as chitosan, carbopol, and pectin, to increase drug delivery. These issues include inconsistent release profiles, suboptimal polymer combinations, and poor in vitro correlation (Teruel *et al*., 2020). Recent progress has been made in MDDS for UC treatment, but there are still challenges to developing a formulation with optimal drug release profiles and formulation consistency (Vande Casteele *et al*., 2021). Many studies have not systematically optimized key parameters, such as polymer concentration, drug load, and particle size, and therefore, outcomes were suboptimal. Standardized designs (such as Design of Experiments — DoE) do not exist, precluding the rigorous evaluation of formulation variables and their interactions and resulting in poor efficacy, safety, and patient compliance (Lombardo *et al*., 2022). These issues require further research.

This research will optimize the mucoadhesive drug delivery system for UC by improving localized drug delivery of mesalamine, reducing the side effects, and improving the therapeutic outcome. It will provide a reliable formulation framework for future formulations by using DoE and ANOVA and improve patient adherence. Broad gastrointestinal drug delivery will also benefit from the findings in developing targeted therapies for other disorders.

1.1 Research questions

- What mucoadhesive formulations could offer for mesalamine delivery and retention in the colon for UC treatment?
- Which formulation parameters (polymer type, concentration, drug load, particle size) give optimal drug release and mucoadhesion?
- What does the optimized formulation do to reduce side effects and improve therapeutic outcomes for UC?

1.2 Objectives

The primary objectives of this research are to:

- The formulation of a mucoadhesive drug delivery system for mesalamine will be optimized to increase drug retention at the colonic mucosa and release the drug in a sustained manner.
- Evaluation of the mucoadhesion and drug release of the formulations systematically as a function of formulation parameters (polymers and concentration, drug load, particle size) using Design of Experiments (DoE) tools.

- Achieve better reproducibility and consistency of drug release profiles, particularly by making in vitro results better correlates of in vivo performance.
- Developing a system to improve the 'therapeutic efficacy' of mesalamine in the treatment of UC through 'decreasing side effects', 'decreasing dosing frequency', and 'increasing patient compliance'.

2. Literature Review

Mucoadhesive drug delivery systems (MDDS) for ulcerative colitis (UC) demonstrate promising developments in the use of mesalamine as an existing treatment for UC coupled with multiple different mucoadhesive polymers such as chitosan, carbopol, and pectin (Kulkarni *et al*., 2023). The potential of these polymers in increasing drug retention and controlled release at the colonic site of action. Current studies suffer from the problems of inconsistent drug release profiles, suboptimal use of polymer combinations, and poor in vitro correlation (Yan *et al*., 2022). Drug release as a function of key formulation factors, such as polymer concentration, drug load, and particle size, has not been systematically optimized. Many studies do not employ statistical methods such as Design of Experiments (DoE) to direct formulation improvements (Asha *et al*., 2020). The gaps in understanding and the lack of suitable polymer formulations for these applications are addressed through systematic DoE-based optimization of formulation parameters, and exploring new combinations of polymers (Sameina *et al*., 2023). The aim of this research is to improve the reproducibility of formulations, increase drug release consistency, and obtain better, more physiologically relevant in vitro results. This research will apply statistical tools, ANOVA, to identify the optimal formulation for sustained mesalamine release. These findings would be useful in generating improved and patient-friendly management of UC with enhanced short interval dosing and fewer adverse effects, higher therapeutic effect and higher patient compliance. Besides, it will also provide a deeper understanding of its extension into 'mucoadhesive systems for targeted drug delivery' as a therapeutic strategy for gastrointestinal diseases.

3. Methodology

3.1 Pre-formulation Studies

During the pre-formulation stage, both the drug and the excipients' physio-chemical properties regarding their pharmacokinetics and performance in a mucoadhesive matrix and drug delivery of an optimal amount will be assessed.

- Drug Candidate Selection: Mesalamine is chosen and in its treatment of Ulcerative colitis treatment it has met the criteria involving molecular weight, pKa solubility and stability.
- Excipients Selection: This matrix will be prepared from polymeric materials and additives which are responsive to the colonic mucosae, including chitosan, carbopol, and pectin.
- Drug-Excipient Compatibility Testing: ''Fourier Transform Infrared Spectroscopy (FTIR)' and 'Differential Scanning Calorimetry (DSC)' instrumentations will be applied to assess the compatibility of the drugs and excipients to ensure both stability and efficacy).

Timeline: The completion of this phase takes 2 to 3 months.

3.2 Formulation Development

Mucoadhesive drug delivery system will be designed and it will be planned according to a proper formulation to select microspheres, nanoparticles or hydrogels for adhesion to colonic mucosa and for the extension of drug release period.

- Polymer Selection and Ratios: Different types of mucoadhesive polymers and their ratios will be tested to optimize adhesion and drug release.
- Encapsulation Techniques: The drug will be encapsulated by techniques such as ionic gelation or solvent evaporation characterized according to the formulation type.
- Formulation Optimization: The parameters such as polymer concentration, drug load, and particle size will be refined using a design of experiments (DoE) approach such as factorial design or response surface methodology.

Timeline: This will take roughly 3 to 4 months.

3.3 In Vitro Evaluation

In the in vitro phase, mucoadhesive properties, drug release profile and stability of the manufactured formulation in a simulated colonic fluid will be determined.

- Adhesion strength will be evaluated using excised colonic tissue or mucin-coated slides as a colonic mimic using a texture analyzer.
- Drug Release Studies – Drug release will be carried out in a simulated 'colonic fluid environment (pH 6.8)' using a dissolution apparatus, to monitor the drug release profile over time. The drug release data will be analyzed and fitted to kinetic models, such as 'zero order', 'first order', 'Higuchi', and 'Korsmeyer-Peppas models', to elucidate the drug release mechanism.

Timeline: This will take 2 to 3 months approximately.

3.4 Statistical Analysis and Optimization

The impact of these formulation parameters on outcomes of adhesion, release, and efficacy will be evaluated using statistical tools such as ANOVA. The in vitro evaluations will refine the formulation to achieve maximum therapeutic effect, optimum sustained release, and minimum side effects.
Timeline: This phase will take 1 to 2 months.
Overall Timeline: 8-12 months

The mucoadhesive drug delivery system will be optimized through iterative optimization of the mucoadhesive system, which will be accomplished through 8 to 12 months of research, consisting of approximately 8 months of pre-formulation studies, formulation development, and in vitro evaluation of the formulations, followed by statistical analysis.

4. Justification

4.1 Pre-formulation Studies

To ensure that the drug and excipients are stable, compatible, and able to maintain pharmacokinetic efficacy, a formulation with the stable drug is required to deliver the drug effectively to its intended site. The drug candidate chosen is mesalamine, which is an effective drug in treating ulcerative colitis and has good molecular properties such as molecular weight, pKa, solubility, and stability, making it suitable for localized colonic delivery. The selected excipients being used as mucoadhesive polymers, such as chitosan, carbopol, and pectin, aid in therapy, increasing retention time at the mucosal surface and thus providing prolonged exposure to the colonic tissue. Compatibility testing is performed using FTIR and DSC to rule out the possibility of interactions (between drug and excipients) that may affect stability or efficacy and to see if the excipients will degrade or chemically change the drug.

4.2 Formulation Development

Different polymers and their ratios are tested to optimize mucoadhesion and drug release rates, which are critical for maximizing retention time and bioavailability at the target site. Microspheres, nanoparticles, or hydrogels are created using techniques such as ionic gelation and solvent evaporation to support the controlled, sustained release of drugs. However, to refine these formulations, a Design of Experiments (DoE) approach, such as factorial design, can be used to systematically study formulation factors including polymer concentration, drug load, and particle size, and precisely optimize for maximum therapeutic effectiveness.

4.3 In Vitro Evaluation

By testing adhesion strength on excised colonic tissue or mucin-coated slides, able to predict the adhesion capability and drug localization potential of the formulation in vitro. To further mimic the colonic environment, drug release studies in simulated colonic fluid (pH 6.8) are conducted to assess how consistently and effectively the formulation releases the drug over time. The release data is analyzed using kinetic models, such as zero order, first order, or Higuchi, to obtain a better understanding of the release mechanism, and to achieve sustained and controlled drug delivery.

4.4 Statistical Analysis

In this study, ANOVA is selected because it can analyze multiple formulation factors such as polymer concentration and particle size, and their interactions on the outcomes of mucoadhesion and drug release. It is perfect for complex experimental designs such as Design of Experiments (DoE), as it lets us determine statistically significant differences across formulations, controlling error rates. Furthermore, ANOVA's results can be further refined with posthoc tests, which can make clear the formulations that differ, and help in precisely optimizing the 'drug delivery system'.

5. Conclusion

Concept of mucoadhesive drug delivery system (MDDS) for the development and optimization of mesalamine offers the best solution to the issues of UC treatment. This approach addresses the problem of weak drug targeting, inadequate and irregular drug release profile and system wide side effects by incorporating mucoadhesive polymers such as chitosan, carbopol and pectin. This research enhances drug targeting and retention at the colonic site together with the enhancement of the drug release rate constant through the adjustment of critical formulation parameters utilizing Design of Experiments (DoE). The outcome is more efficient and productive treatment less side effects, less frequent dosing, and increased compliance. The formulation is further optimised to ensure the best reproducible and constant release profiles with the aid of statistics (ANOVA). These results contribute to the treatment of UC and offer a model of targeted drug delivery for other GI diseases – demonstrating how designing relevant drug delivery systems greatly optimizes treatment safety and efficacy, as well as patient adherence.

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Formulating mucoadhesive drug delivery systems in various forms such as tablets, capsules, or others:

Selection of Mucoadhesive Polymers
Chitosan, carbopol, and pectin should be used because they have been pointed out for their efficiency in enhancing drug entrapment and maintaining the controlled release in the colonic site. The polymers to be used and their proportion should be selected based on the requirement of the drug release rate and mucoadhesive property.

Drug-Excipient Compatibility
Carry out compatibility checks of the drug, for instance,e mesalamine, and the outchosen excipients for the pharmaceutical formulation. This could just be achieved by fantastic analytical tools such as Fourier Transform Infrared Spectroscopy (FTIR) as well as Differential Scanning Calorimetry (DSC).

Formulation Techniques

Tablet Form
Direct compression with mucoadhesive polymers can be used to develop sustained-release tablets. Granulation may be necessary for enhanced compaction and distribution of the drug.

Capsule Form
For better administration and controlled release, drug-polymer mixtures should be encapsulated in hard gelatin or hydroxypropyl methylcellulose capsules.

Microspheres/Nanoparticles
Some of the methods include; ionic gelation or solvent evaporation depending on whether you are creating microspheres or nanoparticles. These forms may provide a tighter fit and faster disintegration coupled with possible better retention and a more controlled drug release rate.

Example Formulation Data
The following table provides a framework for key formulation parameters across different dosage forms:

Formulation Parameter	Tablet Form	Capsule Form	Microspheres/Nanoparticles
Polymer Type	Chitosan	Carbopol	Pectin
Polymer Concentration (%)	10	15	20
Drug Load (%)	20	30	25
Particle Size (µm)	-	-	200
Encapsulation Technique	Direct compression	Filling (pre-mixed)	Ionic gelation
Mucoadhesion Strength (N)	1.5	1.8	2
Drug Release Time (hrs)	12	16	24
Drug Release Profile	Zero-order	Higuchi	Korsmeyer-Peppas
Stability (days in colonic fluid)	7	10	14

Optimization using Design of Experiments (DoE)
Implement a Factorial design or Response Surface Analysis to systematically and systematically control and enhance polymer concentration, drug loading, and particle size for instance. This guarantees a formulation with the highest possible therapeutic value.

In Vitro Evaluation
Carry out investigations to determine mucoadhesion strength, drug release characteristics, and stability under conditions that mimic the colon (pH 6.8). The release data of the drug should be analyzed by kinetic equations in order to determine the release mechanism.

Scale-Up Considerations
The final critical control point is therefore determining the level of consistency, both at the batch level and also at the manufacturing process level when the formulation parameters have been optimised.

Plan of Work

1) Pre-formulation Studies (2-3 months)
- **Drug Selection**: Based on their favorable pharmacokinetic properties (molecular weight, pKa, solubility, and stability), mesalamine is selected for targeted colonic delivery in UC.
- **Excipient Selection**: Chitosan, carbopol, and pectin will also be used as mucoadhesive polymers to enhance retention and controlled drug release at the colonic site.
- **Compatibility Testing**: The stability and compatibility of mesalamine with selected excipients will be assessed by FTIR and DSC.

2) Development of Formulation (3-4 months)
- **Polymer Selection & Ratios**: Optimal mucoadhesion and drug release will be tested in various combinations of polymers.
- **Formulation Types**: Direct compression, encapsulation, and ionic gelation/solvent evaporation will be investigated for tablets, capsules, microspheres, and nanoparticles.
- **Optimization:** The polymer concentration, drug load, and particle size will be optimized using a Design of Experiments (DoE) approach.

3) Evaluation in Vitro (2-3 months)
- **Mucoadhesion Testing**: The adhesion strength of the adhesion element will be evaluated on excised colonic tissue or mucin-coated slides using a texture analyzer.

- **Drug Release Studies**: In vitro release will be performed in simulated colonic fluid (pH 6.8) and kinetic models (zero order, first order, Higuchi, Korsmeyer Peppas) will be used to analyze release.

4) Statistical Analysis and Optimization (1-2 months)

- **Data Analysis**: The effects of formulation variables (polymer concentration, drug load, etc.) on mucoadhesion, release, and efficacy will be studied using ANOVA to determine significant effects.
- **Optimization:** Based on these statistical findings, iterative adjustments to the formulation will be made to maximize the therapeutic effect while minimizing side effects.

5) Scaling Up & Regulatory Considerations (ongoing).

- **Scale-Up:** The formulation is optimized to ensure batch consistency and manufacturing process reliability.
- **Regulatory Considerations:** Discussions at an early stage as to which regulatory pathways should apply for the approval of clinical trials involving preclinical data and pharmacokinetic analysis.

In Vivo Analysis (Toxicological Analysis Study and Animal Study)

1) Acute Toxicity Study (1 month)

Objective: The immediate toxicity of the mucoadhesive drug delivery system was assessed and the safe dose range for further testing was determined.

Method:

- **Animal Selection:** Wistar rats or CD-1 mice will be used as rodents. A total of at least 6 animals per group will be randomly assigned to different dosage levels of the formulation.
- **Dosing:** Oral gavage or intraperitoneal injection of the mucoadhesive formulation for administration in single or multiple doses, as appropriate for the intended clinical route of administration.
- **Monitoring:** Animals will be observed continuously for the first 4 hours post-administration and daily for 14 days.
- **Parameters Monitored:** Mortality, clinical signs (e.g., lethargy, aggression, fur loss), body weight changes, food/water consumption, and any gross behavioral changes.
- **Organ Analysis:** At the end of this observation period, animals will be euthanized, and key organs (liver, kidney, heart, lungs, and gastrointestinal tract) will be examined histopathologically to detect acute damage.
- **Outcome Measures:** From these observations, the LD50 (lethal dose for 50% of the population) will be estimated, as will the No Observed Adverse Effect Level (NOAEL).

2) Sub-Chronic Toxicity Study (2-3 months)

Objective: These studies were carried out to determine the long-term safety profile of the formulation (toxicity and organ-specific effects).

Method:

- **Animal Selection:** For subchronic toxicity, Wistar or Sprague Dawley rats at 10–12 animals per group will be used.
- **Dosing:** For the chronic toxicity study, the formulation will be given orally using the same route as in the acute toxicity study, but over a prolonged period of 30 to 90 days.
- Dose-dependent effects will be tested using different dosages, low, medium, and high.

Monitoring:

- **Clinical Observations:** Regular monitoring for signs of toxicity includes gastrointestinal distress, lethargy, weight loss, and organ-specific symptoms.
- **Blood Chemistry:** Blood sampling for weekly changes in liver (ALT, AST, bilirubin), kidney (creatinine, urea), and other organ markers (e.g., glucose and proteins).
- **Urine Analysis:** Routine checks for kidney function via urine output and specific gravity.
- **Histopathology:** At the end of the study, tissues will be harvested to analyze for morphological and histological changes in the liver, kidney, lung, heart, brain, and intestines.
- **Outcome Measures:** Then, we will focus on identifying cumulative toxicity, organ dysfunction, or histopathological damage. A major emphasis will be on determining safe dosage levels for long-term use.

3) Immunogenicity Study (1-2 months)

Objective: The immune response induced by the mucoadhesive formulation should be investigated, with special reference to allergic reactions or inflammation.

Method:

- **Animal Selection:** At least 6 animals per group of healthy rats or mice will be used.
- **Dosing:** The mucoadhesive formulation will be administered in repeated doses either daily or every other day for up to 28 days.

Monitoring:

- **Immune Response Indicators:** Periodically, blood samples will be taken to measure cytokine levels (IL-6, TNF-alpha, and IFN-gamma) IgE, and antibody titers. Any systemic immune activation will be evident by these markers.
- **Histopathological Examination:** Investigating and identifying organs with signs of immune cell infiltration or inflammation of key organs (lymph nodes, spleen, intestines, liver).
- **Clinical Observations:** Local inflammation at the injection site or systemic allergic reaction (e.g., rash, swelling, respiratory distress) will be observed.
- **Outcome Measures:** The study will look for any immune-mediated side effects such as chronic inflammation or allergic sensitization.

4) Pharmacokinetic Study (2 months)

Objective: The bioavailability and colonic retention of mesalamine delivered by the mucoadhesive formulation compared to conventional methods of delivery were determined.

Method:

- **Animal Selection:** At least 6 animals per group will be used, rodents (Wistar rats or Sprague-Dawley rats).
- **Dosing:** The formulation will be administered in mucoadhesive formulation as well as in a conventional mesalamine oral tablet.
- **Sampling:** At various time points (e.g., 1, 3, 6, 12, 24, and 48 hours) after drug administration, blood samples will be collected.
- **Plasma Mesalamine Concentration:** Mesalamine concentrations will be measured in plasma and analyzed by High-Performance Liquid Chromatography (HPLC).
- **Colonic Tissue Analysis:** Animals will be euthanized at the end of the sampling period and mesalamine concentration in the colonic tissues will be measured by similar HPLC methods.

Outcome Measures:

- **Bioavailability Comparison:** The mucoadhesive formulation will be compared to conventional treatment concerning Cmax (maximum concentration), Tmax (time to reach Cmax), and AUC (area under the curve).
- **Retention:** Mesalamine concentration in colonic tissue will also give an insight into the mucoadhesive formulation's drug targeting and retention ability in comparison to the conventional formulation.

5) ANIMAL MODEL FOR EFFICACY (2-3 months)

Objective: The therapeutic efficacy of the mucoadhesive drug delivery system was also evaluated in a disease model of ulcerative colitis (UC).

Method:

- **Animal Selection:** The chronic inflammation and ulceration of UC can be simulated by using an appropriate UC model (for example, DSS-induced colitis in rats or mice).
- **Dosing:** The oral mucoadhesive formulation will be compared with a placebo or with conventional mesalamine treatment.
- **Disease Induction:** Administration of DSS (dextran sulfate sodium) or other inducers of colonic inflammation will induce UC.

Monitoring:

- **Clinical Signs:** Observation for weight loss, diarrhea, blood in feces, and general condition every 6 months.
- **Histopathology:** After death, they will harvest colonic tissues and look for evidence of ulceration, inflammation, and tissue damage.
- **Biomarkers:** Blood and colonic tissue will be measured for UC-specific biomarkers such as pro-inflammatory cytokines (e.g., IL-1, TNF-α, IL-6), etc.
- **Outcome Measures:** This will be assessed for therapeutic effect based on reduction in disease markers like inflammation as seen in tissue and ulceration and pro-inflammatory cytokine levels. Clinical symptom improvement and histopathological recovery will be compared between the mucoadhesive formulation and placebo, as well as conventional treatments.