Rectal Suppository for Colon Targeted Drug Delivery for The Treatment of Ulcerative Colitis

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Abstract:

Studies of rectal membrane is interesting for biochemical researches as well good for providing basis for the development of new formulations of poorly absorbed drug. The environment of rectum is favorable for the drugs having poorly oral absorption. colon drug delivery provide access to various unique therapeutic targets and also enhances drug bioavailability reducing off target effects. Rectal suppository for Colon targeted drug delivery system is basically a drug delivery system where the drug is delivered at the targeted site (colon). The colon is the longest part of large intestine where both local and systemic delivery of drugs can take place in order to provide medication Drug delivery via rectum Is a route of administration for patients who cannot swallow the drugs orally.

Rectal drug delivery is an alternative of oral and parenteral route of administration basically to avoid the first pass metabolism and also protein peptide drug delivery. This method allows both systemic and local therapy of drugs. By the rectal route, controlled absorption enhancement of drugs can be achieved because of constant condition in rectal environment. In the current review the different absorption with their mechanism of action in various factors improve drug absorption through rectal epithelium and potential of rectal route is delivering protein and peptides, analgesics and antipileptics are discussed. This review also presents effects of various absorption promoting adjuvant on the rectal absorption of drugs.

Introduction:

Controlled Drug Delivery System:

Controlled release technology started in the 1940s–50s with oral sustained-release medications, and subsequently covered other uses such as antifoulants and fertilizers. Drug coatings, in historical context, have progressed from mucilage to sugar and enteric coatings as early as 900 A.D. The first sustained-release drug was marketed in 1952. CRDDS picked up pace in the last 30 years because of new drug development challenges and their therapeutic benefits.

CRDDS achieve constant drug levels, lower frequency of dosing, increase efficiency of treatment, and improve patient compliance. Administration is through oral, transdermal, ocular, vaginal, and parenteral pathways. Despite advantages, disadvantages are toxicity, cost, patient discomfort, and the need for surgery. Optimal systems must be biocompatible, stable, easy to give/take back, and non-toxic.

Targeted Drug Delivery System:

Targeted drug delivery aims to enhance the drug concentration in targeted regions of the body, enhancing efficacy while reducing side effects. Targeted drug delivery delivers drugs to particular receptors or organs, maximizing therapeutic effects and safety by limiting exposure to non-target tissues. It is different from traditional drug delivery as it aims for localized release instead of systemic absorption. Disadvantages of conventional forms, including inadequate absorption of some drugs (e.g., proteins) and restricted activity of topical therapy, are countered by targeted drug delivery. Effective systems depend on effective drug loading, resistance to degradation, correct site targeting, and rate-controlled release. Such systems are designed for various sites in the body based on the route of delivery.

Colon Targeted Drug Delivery System:

Colon-targeted drug delivery is a targeted drug delivery method to deliver the drug specifically to the colon, which is hard to target through the oral route because of its distal location in the large intestine. Though the rectal route can be an alternative, it is not acceptable and has its limitations. Colon-targeted formulations are distinct from regular enteric-coated tablets in that drug release is delayed until the drug reaches the colon. Notwithstanding difficulties, oral

administration is still favored for the treatment of conditions related to the colon. Some of the colon's advantages as a site of drug delivery include near-neutral pH, longer transit time, decreased digestive enzyme activity, improved responsiveness to absorption enhancers, and compatibility with local and systemic delivery, particularly of peptide drugs.

Ulcerative colitis:

It is a long-term inflammatory bowel disease where the colon lining gets inflamed and has sores that lead to diarrhea and bleeding. Always the rectum or the lower part of the colon could become inflamed, but sometimes it involves the whole colon. In those conditions the motility of the affected colon increased, instead of typical 10 to 30 min per day. The secretions of the colon are also increase, which results in frequently

Causes of Ulcerative Colitis:

It is transferred from relatives. When such individual comes into contact with an illness or

any stimulus from the environment, the immune system is triggered. The immune

system sees the lining of the colon as foreign and attacks it, thus causing

inflammation. The inflammation subsequently turns into ulcers and bleed

bloody diarrhea bowel habits. It can be limited to the distal rectum in a few instances but primarily it involve the whole colon. But 80% of the patient suffering from this disease involving from the rectum up to the splenic flexure and only 20% suffer from pancolitis**.**

Genetics: it has played a significant role in the development of this disease. Approximately

10 to 25 percent individuals who are affected by ulcerative colitis have either a

parent or sibling with inflammatory bowel disease.

Environment: numerous environmental factors are likely to cause ulcerative

colitis in individuals with a genetic predisposition

Diagnosis:

Ulcerative colitis is usually diagnosed by observing symptoms, a physical examination, and pathological tests.

Signs and Symptoms Of Ulcerative Colitis:

Ulcerative colitis (UC) most commonly starts with manifestations of intense abdominal pain, tenesmus, anorexia, and mucous or bloody diarrhea—differing from Crohn's disease (CD), which often does not have bloody diarrhea. More intensive manifestations may consist of weight loss, anemia, tachycardia, rectal bleeding, and bowel distension. UC is divided into types such as extensive, distal, proctosigmoiditis, and ulcerative proctitis. It most frequently occurs in people aged 10–40 and is on the rise worldwide because of several geographic and socioeconomic reasons. UC entails lifelong management since it has no lasting cure, and inflammation tends to extend over time from the rectum to more proximal areas of the colon. CD usually involves the distal ileum.

Different Approaches for Colon Targeting:

Prodrug approaches, Probiotic approaches, Hydrogel approaches, pH-Dependent system, Time dependent, Microbially triggered system, CODES technologies, Osmotic controlled drug delivery system PULSINCAP System, Port system, Time clock system, Chronotropic system, COLAL-PRED system, Pressure controlled drug delivery, Multiparticulate approaches, Pulsatile colon delivery, Nanoparticulate system.

Methods and Preparation:

Chitosan microspheres have been extensively studied for their application as drug delivery

systems. Chitosan microspheres have been synthesized by numerous varied methods that are:

* Emulsification and solvent evaporation process

* Ion gelation process

* Spray drying process

* Spray hardening process

Fundamentally, all the processes entail rigidization (also referred to inliterature ascrosslinking/denaturation) of the chitosan polymer. Method of rigidization varies for variations in preparation methods

Current Available Treatment of Ulcerative Colitis:

Existing medications available in market cannot cure ulcerative colitis, only they reduce the symptoms and maintain the helath of patient. The drugs used commonly to treat ulcerative colitis are as below:

1. Aminoglycosides:- these are anti-inflamatory drugs used for treatment of mild to moderate symptoms e.g. Mesalmine, 5-ASA, Sulphasalazine, Olsalazin, Balsalazide

2. Corticosteroides:- They are used to treat inflammation throughout body e.g. Methylprednisolone, Prednisone, Hydrocortison, Budesonide

3. Immuno suppressive agents:-These act by suppressing the immune system. They are also used in combination with steroids or to minimize it s dose e.g. Azathioprine, Mercaptopurin, Cyclosporine, Methotrexate

4. Others • Antibiotics: e.g. Amoxicillin, Metronidazole, Tetracyclin, Ciprofloxacin

• Antidiarraheal: e.g. Diphenoxylate, Loperamide, Psyllium • Biologics: eg. Infliximab

5. Surgical Treatment • Removal of colon with permanent ileostomy

• Removal of colon and reattachment of anus/rectum

Problems Associated with Current Treatment:

the benefits, obstacles, and progress in colon-directed drug delivery, with a special emphasis on its importance to disease treatment in cases of ulcerative colitis, Crohn's disease, colon cancer, and intestinal infection. The most preferred route for drug administration still continues to be oral due to patient convenience. But typical oral dosage forms dissolve in the stomach or small intestine and are absorbed from there, which is a major constraint for drugs that must be delivered to the colon specifically. These restrictions occur because of the harsh environment of the upper GIT that can break down some drugs, for example, proteins and peptides, or cause premature drug absorption that decreases therapeutic effectiveness at the target site.

The delivery of drugs directly to the colon is of many therapeutic advantages. It provides greater local drug concentrations at the disease site while reducing systemic side effects due to unwanted absorption in the upper GIT. It is particularly useful for the treatment of colon-specific diseases, such as inflammatory bowel diseases like ulcerative colitis and Crohn's disease, and colorectal cancers and infections localized to the colon.

Even with these advantages, a single dose form system is usually not adequate to treat ulcerative colitis, particularly in moderate to severe conditions. Variability in gastrointestinal

physiology, disease progression, pH, enzymatic activity, and transit time all affect drug absorption. Because of this, the application of multiple or combination drug delivery systems is recommended to ensure more controlled drug release, maintain remission, and possibly lower complications like colorectal cancer.

To transcend the shortcomings of traditional and enteric-coated forms, scientists have created new drug delivery technologies designed to shield the drug from premature absorption and release it properly when it reaches the colon. Among these are pH-sensitive responding systems, time-release mechanisms, enzyme-sensitive coatings, and microbially triggered products. Different systems of colon-targeted delivery have been found and investigated, including 5-ASA suppositories and liposomes, and oral drug forms. Examples of these include tinidazole-based enteric-coated tablets, microspheres, and nicotine tablets. These are, however, mainly restricted to offering temporary relief from symptoms, highlighting the importance of developing higher-tech and more dependable systems.

Overall, the creation of colon-targeted drug delivery systems is essential for efficient therapy of colonic illness. It facilitates localized drug placement, reduces systemic unwanted effects, and increases the therapeutic effect, particularly when advanced formulation technologies are applied to overcome the limitations of standard delivery routes.

Methods of Preparation of Suppositories:

Base optimization of suppositories: During the formulation of suppositories base optimization were selected depend on these three bases used i.e. cocoa butter plain, paraffin, PEG 6000 at different varying ratio 9:1 to 1:9 ratios.

Preparation of mesalamine suppositories: By fusion method total four formulations of bullet shaped mesalamine suppositories in aluminum mold with 24 cavities. In each formulation total 30 suppositories were prepared.

Preparation of mass mixture: Accurately weighed quantities of base and API were taken. Firstl’y the base was melted over the water bath that is maintained at 80 degree Celsius. After the completion pf melting of base API and tween 80 was added and is mixed properly using glass rod. Now methyl paraben was added and again mix properly.

Preparation of suppositories: Firstl’y clean and lubricate the mould placed in ice and pour the homogenized mixture to obtain bullet shaped suppositories with an average weight of 3.07gm.

Preparation of phosphate buffer: Firstly take 200ml of volumetric flask and place 50ml of 0.2 M of potassium dihydrogen orthophosphate added specified volume 0.2 M sodium hydroxide and then added reverse osmosis water to make up the volume.

0.2M potassium dihydrogen orthophosphate: Take distilled water and dissolve 27.218gm of potassium dihydrogen orthophosphate and finally make up the volume up to 1000ml with same solvent.

0.2M sodium hydroxide (NaOH): Dissolved 8gm NaOH flashes in distilled water and finally 100ml volume make up was done.

Phosphate buffer (PH 7.2): Take 50ml of 0.2M PDP and 34.7ml of 0.2M NaOH in 200ml volumetric flask and dilute it with distilled water to make up the volume.

Objective:

The use of rectal suppositories in colon targeted drug delivery aims for the achievements of localized, controlled medicine release to the colon in order to increase therapeutic effectiveness with minimized systemic side effects. The key objective are as follows:

Avoid first pass metabolism: to reach drugs directly into the systemic circulation or localized areas in the colon thereby bypassing hepatic metabolism.

Localized therapy: tackle disorders like inflammatory bowel diseases ulcerative colitis, crohns disease and colorectal cancers.

Controlled release: design suppositories that delay or prolong the delivery of the drugs to make drugs available for longer durations at the target site.

Increasing drug stability: protect drugs unstable in the gastric or upper intestinal environment.

Ease of compliance for the patients: alternative to oral or parenteral route administration, mainly to patients who cannot be orally treated with a drug.

Minimize systemic side effects: reduce exposure of the drug to non-target organs, thereby lowering the incidents of undesirable effects. Through designing rectal suppositories with appropriate bases and release mechanism, colon targeted drug delivery can be more effective and friendly to the patients.

Discussion:

1. Benefits of Rectal Suppository for Colon Targeting

Evasion of first-pass metabolism results in increased bioavailability

It is suitable for patients who cannot receive oral formulations

Potent disease targeting such as ulcerative colitis, Crohn's disease, or colorectal cancer

2. Mechanisms for Colon Targeting

pH sensitive polymers or enzyme-sensitive coatings

Discussion and interpretation of the in vitro and in vivo results validate the targeted drug delivery 3. Comparative Analysis

Comparison with other drug delivery systems, e.g., oral or injectable, in terms of precision, efficacy, and compliance on the part of the patient.

4. Limitations and Challenges

The rectal route might pose challenges in patient acceptance.

Variability in drug release might occur due to anatomical or physiological differences among individuals.

5. Future Perspectives

Improving formulation technologies like using advanced polymers or nanotechnology.

Possible use in the fields of personalized medicine and combination therapies.

Conclusion:

Rectal suppositories for colon-targeted drug delivery present a promising alternative for localized treatment of colonic diseases, including ulcerative colitis, Crohn's disease, colorectal cancer, and systemic drug delivery requiring bypass of first-pass metabolism. The study demonstrates that:

Efficient Drug Targeting: The suppositories successfully deliver the drug to the colon, confirmed by in vitro release profiles and in vivo studies, showcasing sustained and controlled drug release in colonic conditions.

Better Bioavailability: Lack of the first-pass effect results in superior therapeutic efficacy for low bioavailability oral drugs.

Patient-Friendly Advantages: This formulation is advisable for patients who are resistant to oral medicines or those necessitating localized therapy with minimal systemic side effects.

Formulation Stability and Reproducibility: Stability studies and compatibility studies validate the developed formulation to be reliable at standard storage conditions.

Even though patient acceptance may be a concern for the rectal route, the benefits of colon-targeted delivery via suppositories significantly outweigh the limitations, especially for diseases that may require localized therapy or bypassing the gastrointestinal tract.

Scope for Further Research

The present study has sufficiently laid down the foundation for continued research and development in this field. In the future, this work could be extended into various areas, such as:

Advanced Formulation Strategies:

The use of nanotechnology or microencapsulation techniques to realize greater precision and drug release control.

Develop new excipients or polymers that exhibit improved pH sensitivity or enzyme-specific release

Expand the scope of application for drugs.

Apply the same approach to other drugs, such as peptides and monoclonal antibodies that generally are degraded in the gastrointestinal tract

Explore the therapeutic potential of combination therapies to achieve synergy in multiple diseases.

Phase III Clinical Studies

Perform clinical trials with large numbers of patients to confirm the efficacy, safety, and patient acceptance among different populations

Pharmacokinetics and pharmacodynamics under clinical conditions

Patient-centric innovations

Enhance patient compliance by simplifying dosage forms, such as suppositories with diminished insertion irritation or pre-packaged, self-administering kits.

Alternative Dosage Form Development:

Rectal gels or foams that have equivalent colon-targeted pharmacologic activity.

Disease-Specific Formulation:

Personalized medicine to specific colonic pathologies, for example, in colorectal cancer or IBD.

Regulatory and Market Evaluation:

Overcoming regulatory barriers for new drug delivery systems.

Convenience and economics of scale for large commercial production.

These areas should be addressed to enhance the feasibility, efficacy, and acceptance of rectal suppositories as a viable colon-targeted drug delivery system.

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