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POTENTIAL ADJUVANTS IN DRUG FORMULATION FOR COLON SPECIFIC DRUG DELIVERY SYSTEM

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ABSTRACT

Modern drug delivery techniques for the colon receive analysis because they provide vital therapeutic options to treat inflammatory bowel disease alongside other colon-based medical conditions. Drug product development succeeds because of understanding colon-specific factors including pH values along with microbial content. The research investigates three drug delivery techniques by explaining Prodrugs together with pH-sensitive substances and detection methods for colon bacteria to precisely release drugs. The available techniques enhance the absorption of poorly soluble drugs while minimizing systemic drug adverse responses. The paper identifies new ways to enhance patient outcomes yet the research community must first overcome multiple challenges related to developing secure pharmaceutical products. Better therapeutic treatments that focus on treating colonic disorders in patients require sustained research and innovation efforts.

Keywords: Potential Adjuvants, Colon Targeted Drug Delivery, Ulcerative Colitis, Microparticles, Inflammatory Bowel Disease (IBD).

INTRODUCTION

The colon is an interesting area for both local and systemic medication [17].Various modifiers of colon-targeted drug delivery systems have been considered for the treatment of colonic disorders. These systems improve the solubility of poorly soluble drugs in an alkaline pH environment such as the intestine prevent changes in the drug's release or stability in the delivery system when stomach acid is present, and even miniature yet quite complex systems for targeted releasing with the help of colonic enzymes. But the major contribution is in the complete prohibition of harmful drug constituents to reach the blood circulation through obligatory ingestion, injection, inhalation or absorption through the skin[1].

Currently, over four billion dollars global market is shared by biopolymer based applications like modified, extended, delayed, and targeted drug delivery. However, a large number of potential drugs introduced at the early stages of their discovery do not necessarily directly attract investors, as these compositions can potentially change many times during later proof-of-safety and proof-of-efficacy studies. More sophisticated carriers have been developed for site-specific drug release in the colon, aimed at preventing degradation and absorption of the drug in the first intestine passage, followed by controlled or immediate release in the proximal and distal colons[1].

Anatomy and Physiology of the colon

To effectively target drugs to the colon, it is essential to understand its unique physiological features within the GI tract. The colon, approximately 1.6 m long, consists of the proximal (caecum, ascending, and transverse colon) and distal regions (descending, sigmoid colon, rectum, and anus), with the widest diameter at the caecum (4.7–4.8 cm) and narrowing toward the sigmoid colon before widening again at the rectum. The proximal colon is mobile and suspended by mesentery, while the ascending and descending colon and rectum are retroperitoneal and fixed in place. Key functions of the colon include water, mineral, and vitamin absorption, faecal compaction, polysaccharide digestion, and enteric immunoregulation. The appendix, attached near the ileoceaecal junction, serves as a reservoir for colonic microbiota and plays a role in the enteric immune system, countering the outdated view of it being vestigial[2].

pH environment of the colon

The colon has a pH environment of a healthy individual typically close to neutral, ranging from approximately 6 to 7. But particularly for the duodenum contain pH 6, jejunum 7, ileum contain 7.4 and caecum including proximal colon, distal colon, rectum contain similar pH ranges 6-8[3].

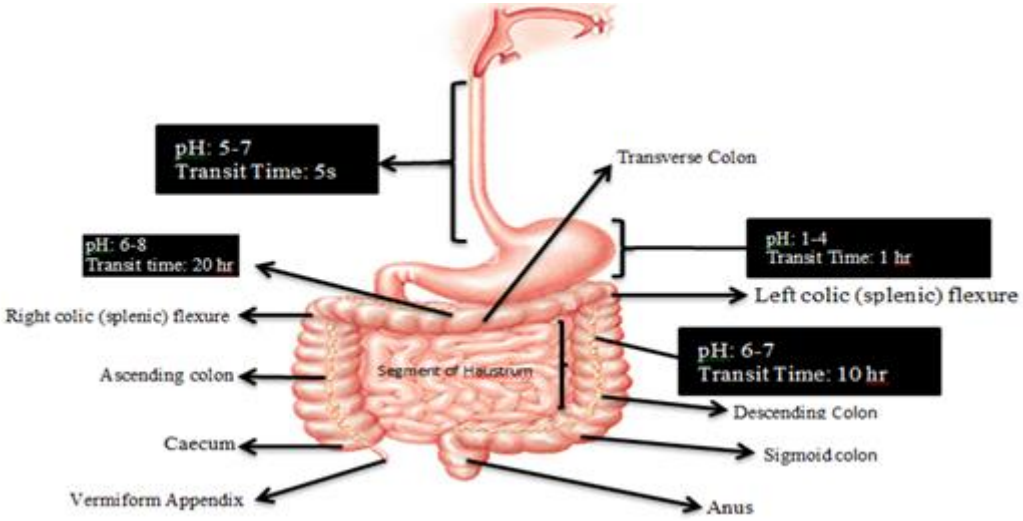

Fig No. 1: Anatomy and Physiology of the colon

Transit time of colon

The transit time of a healthy body has 6-20 hours. But, it can be influenced when the disease occurs such as Inflammatory Bowel disease. Research shows the decreasement of the transit time for the inflammatory bowel disease by 24 hours. [3]

Enzymatic activity[4]

The colon exhibits relatively low proteolytic enzyme activity compare to the upper gastrointestinal tract which create a beneficial environment for drug absorption and minimize the degradation of sensitive pharmaceutics such as protein and peptides.

Vascular and lymphatic network

The colon's oxygenated blood supply comes from the superior and inferior mesenteric arteries and their branches. Deoxygenated blood is drained through the superior and inferior mesenteric veins, which converge to form the splenic vein, eventually leading to the hepatic portal vein. This venous structure affects colon-targeted drug delivery, as drugs absorbed by the colon are processed by the liver, potentially reducing bioavailability. However, drugs administered locally to the lower rectum bypass the liver by entering the iliac veins and then the inferior vena cava, directly reaching the heart. Additionally, drugs can enter systemic circulation via mesenteric lymph nodes (MLNs), particularly lipophilic drugs in lipid-based formulations. The MLNs, which are crucial for the immune function of the colon, drain lymph and play a role in balancing immune responses in the colon, offering opportunities for region-specific immune modulation distinct from the small intestine. [11]

The epithelium

The colon's epithelium lacks villi, but microvilli and folded mucosae increase its surface area significantly, enhancing absorption despite a lower surface area compared to the small intestine. Colonic drug permeability is generally lower, with Biopharmaceutical Classification System (BCS) class I drugs having high bioavailability (>70%), while class III and IV drugs tend to have lower bioavailability (<50%). The colon's epithelial cells are columnar, forming a monolayer connected by tight junctions, with varying permeability between the ascending and descending colon due to differences in claudin expression. The colonic epithelium is constantly renewed, and key cell types include colonocytes, goblet cells, neuroendocrine cells, and immunoregulatory cells. Immune cells in gut-associated lymphoid tissues, like microfold (M) cells and tuft cells, help maintain immune tolerance to gut microbiota and could be targeted for novel vaccines and treatments for immune diseases like inflammatory bowel disease (IBD). [2]

Several strategies can be employed to achieve colon-targeted drug delivery

a. Prodrug approach:

Prodrug approach is mainly considered to have a pre-determined designed to avoid absorption of drug & hydrolysis at the upper part of gastro-intestinal tract, after a while continues to release in the colon because of the favorable pH condition. A study shows an importance of mutual Prodrugs which will be having a very good effect on the treatment of colon diseases where two chemotherapeutic agents having one

active moiety and transporter properties involve as synergistic or additive effect[16,17].

5- ASA and its derivative such as mesalamine, sulfasalazine gives a very effective treatment in the ulcerative colitis[16]. Zhao et al investigated about the amide Prodrug of 4-ASA have a potential effect on the IBD[17].

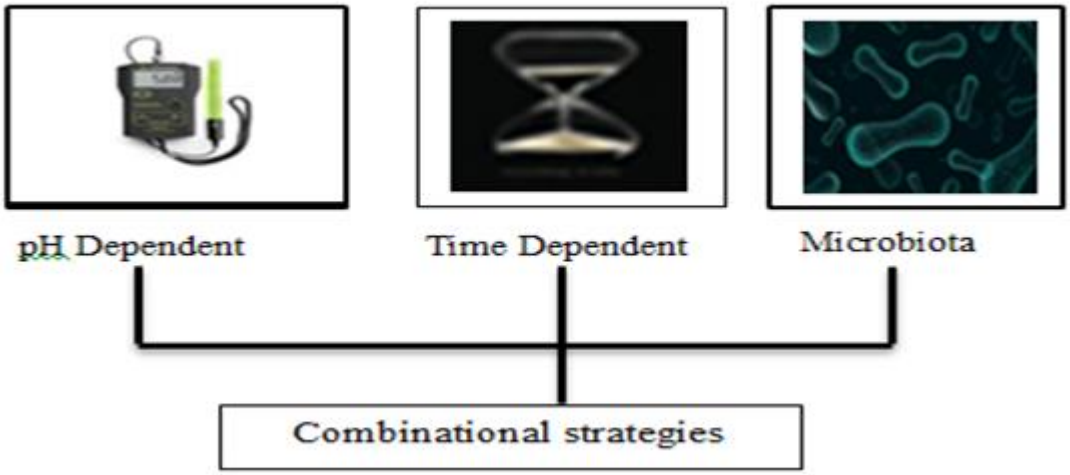

Fig No. 2: Strategies can be employed to achieve colon-targeted drug delivery

b. pH-Dependent Systems

These systems exploit the pH differences between the stomach (acidic) and the colon (neutral to slightly alkaline).89 One of the primary strategies to gain a formulation for colon targeted drug delivery is mainly involving the pH sensitive polymers which response to the different levels of pH overall part of gastro-intestinal tract. pH-sensitive polymers such as Eudragit S 100 used for the controlled and sustained release of catechin for colon targeted drug delivery. [18,19]

c. Time-Dependent Systems

These systems are designed to release the drug after a predetermined time, allowing it to reach the colon. This approach are planned to release the drug at a pre-determined time which allows to release at the site of colon. Here, a research article shows the drug release/ in-vitro parameters of the flurbiprofen core tablets coated for the colon targeted drug release which elaborates that the very minor release of flurbiprofen tablets in the initial lag time continuing with diffused peak for 24 hrs (progressive release) at the specific part of colon. [11]

d. Microbial-Triggered Systems

These systems utilize the unique colonic microflora to trigger drug release. Any formulation contain Prodrugs [29] that are biodegradable by colonic bacteria can be designed. This microbiota triggered systems have very potent effect on the distal part of colon. Studies shows that 400 bacterial species, each having a specific action on the gastro-intestinal tract. Prodrugs or formulations that are biodegradable by colonic bacteria can be designed. For example, polysaccharides like inulin or pectin can be used, which are fermented by gut bacteria, leading to drug release. [28]

e. Enzyme-Responsive Systems

These systems release the drug in response to specific enzymes present in the colon. These systems rely on specific enzymes present in the colon to release the drug. The drug is encapsulated in a polymer that is sensitive to enzymatic degradation, allowing for targeted release when it reaches the colon. Some study shows the drug release profiles of dual sensitive nanoparticles using a polymeric mixture of enzyme- sensitive- azo polyurethane and ph sensitive Eudragit s 100 where coumarin-6 was used as a model drug have found as 100% burst release for inflamed colon. Enzymes such as amylase, pectinase & D-galactosidase can hydrolyze specific bonds within polysaccharides 16 like guar gum, pectin, chitosan & insulin. [31,32]

Diseases related to the colon

Ulcerative Colitis: Ulcerative colitis is a long term inflammatory bowel disease that affects the rectum, causing inflammatory & ulceration of the inner lining. Common symptoms such as

Current Potential Adjuvants for the colon specific for drug delivery

Category	Name of Adjuvant	Properties of adjuvant	Effect on colon disease	Formulation	References
Plant Metabolities	catechin	pH-sensitive therapeutic concentrations of catechin reach the distal parts of the gastrointestinal tract	colorectal cancer and irritable bowel syndrome	Silica nanoparticles	[5]
Active pharmaceutical ingredient	dexamethasone	enhance the therapeutic efficacy of dexamethasone while minimizing systemic exposure and associated side effects	inflammatory bowel disease	Solid dispersions	[6]
Active pharmaceutical ingredient	sulfasalazine	combination ensures that the drug is released specifically in the colon and over an extended period, enhancing its therapeutic efficacy	Inflammatory Bowel Disease	pH-sensitive capsule coating.	[7]
Active pharmaceutical ingredient	mesalamine	Formulations are designed to release mesalamine in the terminal ileum, where the pH is higher than in the stomach and small intestine.	ulcerative colitis	Rectal suppositories	[8]
Active pharmaceutical ingredient	satranidazole	findings indicate that the release profile of satranidazole from these microspheres is pH-dependent	Colon Targeted	Microspheres	[9]
Active pharmaceutical ingredient	Curcumin	pH-dependent	inflamed colon	Microparticles	[10]
API	flurbiprofen	pH and Time dependent	Colon Targeted	Tablets	[11]
API	fexofenadine	Have the properties recover the inflamed intestinal mucosa to the normal condition.	Ulcerative colitis	Solid lipid nanoparticles	[92]
Natural flavonoid compound	Hyperoside	have the potent property to reduce the inflammation	Ulcerative colitis	Mixed micelles	[23]
API	Berberine hydrochloride	Effective to intestine with slow release ability and exhibited anti-inflammatory effects by immune response.	Inflammed colon	Microspheres	[93]

API	Prednisolone (Corticosteroid)	Suppresses immune cell function and cytokine production, thus reducing inflammation.	Systemic effect	Oral tablets, rectal foam, and enemas.	[12]
API	Azathioprine	Suppresses T-cell proliferation by inhibiting purine metabolism, leading to immune system suppression.	Suppresses T-cell proliferation by inhibiting purine metabolism		[13]
API	Budesonide	it works by suppressing inflammatory cytokines, but with less systemic absorption.	Primarily targets the ileum and colon, where its effects are localized.	Oral capsules, rectal foam, and enemas.	[14]
API	Thiopurines (6-Mercaptopurine, 6-MP	Inhibits purine synthesis, leading to suppression of the immune system, which helps to reduce the inflammatory response in UC.	Systemic, affecting immune cell activity in the colon.	Oral tablets.	[15]
Biologic	Infliximab	Neutralizes TNF-α, a cytokine involved in the inflammatory process of UC.	Targets systemic inflammation, including inflammation in the colon.	Intravenous infusion.	[16]
API	Vedolizumab	Blocks the interaction between the integrin α4β7 and its receptor, thereby inhibiting lymphocyte migration to the gut and reducing inflammation.	Primarily targets the gastrointestinal tract, specifically the colon.	Intravenous infusion.	[17]
API	Tacrolimus	Inhibits T-cell activation by blocking calcineurin, reducing the immune response.	Acts systemically, reducing immune-mediated inflammation in UC.	Oral tablets, intravenous infusion.	[18]
Probiotics	VSL	Probiotics restore the balance of gut flora, which can be disrupted in UC, and have anti-inflammatory effects.	Specifically targets the colon by restoring gut microbiota balance.	Oral capsules or sachets.	[19]
API	Etrasimod	Modulates S1P receptors to regulate lymphocyte circulation, thereby reducing inflammation.	Systemic effect with a focus on the gastrointestinal tract, particularly the colon.	Oral tablets	[20]
API	Duvakitug	Inhibits TL1A, a cytokine involved in the inflammatory process of UC.	Systemic effect with a focus on the gastrointestinal tract.	Oral tablets	[96]
API	Tulisokibart	inhibits IL-23, a cytokine involved in the inflammatory process of UC.	Systemic effect focus on the gastrointestinal tract.	Intravenous infusion.	[22]

Marketed products available for colon specific drug delivery

SI no.	Drug	Brand name	Dosage Form
1.	Mesalazine	Asacol	Tablet
2.	Prednisone	Deltasone	Entric-Coated Tablet
3.	Budesonide	Entocort EC	Capsule
4.	Sulfasalazine	Azalfidine	Tablet
5.	Olsalazine	Dipentum	Capsule
6.	Tofacitinib	Xeljanz	Tablet
7.	Ustekinumab	Stelara	Injectable
8.	Vedolizumab	Entyvio	Injectable
9.	Linaclotide	Linzess	Capsule
10.	Fidaxomicin	Dificid	Tablet
11.	Rifaxinsin	Xifaxan	Tablet
12.	Celecoxib	Celebrex	Capsule
13.	Hydrocortisone	Solu-Cortef	Injectable
14.	Vancomycin	Vancocin	Capsule
15.	Metronidazole	Flagyl	Tablet
16.	Oxaliplatin	Eloxatin	Injectable
17.	Bevacizumab	Avastin	Injectable
18.	Adalimumab	Humira	Injectable
19.	Prucalopride	Resolor	Tablet
20.	Balsalazide	Colazal	Capsule

Reference: [97]

abdominal pain, diarrhea often occur with blood & rectal bleeding. The severity of the inflammation can other than among individuals& the condition typically draw a pattern of remission & flare-ups. Though the result is not clear, it is thought to result from an abnormal immune response influenced by environmental factors[81].

Crohn's Disease: Crohn's disease is an another type of inflammatory Bowel Disease that can impact any part of the digestive tract the mouth to the anus, though it most commonly affects the ileum (the end of small intestine) & the colon. It is featured by transmural inflammation, can penetrate the full thickness of the bowel wall. Common symptoms include diarrhea, fatigue, abdominal cramps & weight loss Crohn's Disease[82].

Colorectal Cancer:It is malignancy that evolves in the colon or rectum and stands as of the most causes of cancer-related deaths around the globe. Several risk factors contribute to its development, including advanced age, a family history of the disease & conditions such as ulcerative colitis & Crohn's Disease. Lifestyle factors such as unhealthy diet, obesity and physical inactiveness can also play a significant role on the ulcerative colitis &Crohn's Disease. While early stages of colorectal cancer might not exhibit any symptoms, progression of the disease can lead to noticeable changes in bowel habits, the presence of blood in the stool & sudden

weight loss. Early detection through screening methods, particularly colonoscopy, is vital as it greatly enhances treatment success & patient outcomes[83].

Irritable Bowel Syndrome (IBS):It is a common condition having functional gastro-intestinal disorder that affects gut, often causing discomfort like stomach pain, bloating & gas, along with changes in altered bowel habits, which might causes diarrhea, constipation or alternating between both. Unlike other serious digestive disorders such as inflammatory bowel diseases, IBS doesn't lead to long term damage or inflammation of the intestines. Still, the exact cause of IBS is unclear, but it is believed that factors like hormonal changes, measurement of food in the gut & the body's response to stress can be the causes of IBS[84].

Diverticulitis:Diverticulitis develops when small pouches called diversticula, which can form in the walls of colon and leads to inflammation or infection. This can cause intense abdominal pain, fever, nausea and noticeable changes common for people to have these pouches without any issues (a condition known as diverticulosis), diverticulitis is more serious because, it can lead to complications like abscesses or even perforations in the colon. Managing often involves making dietary changes & during more severe episodes, treatment may also or surgery. or even perforations in the making dietary changes & during more severe episodes, treatment may also require antibiotics or surgery[85].

Colonic Polyps: Colonic polyps are abnormal growth that forms on the inner lining of the colon & can differ in size & type. Although most are benign(non-cancerous) certain kind particular adenomatous polyps, eventually develop into the colorectal cancer, if left unchecked. Routine screening, typically through colonoscopy which is suggested to detect and remove polyps before they develop to cancer. While polyps often cause no symptoms, large or multiple polyps can sometimes leads to bleeding or changes in bowel habits[86].

Ischemic Colitis: A decrease in blood supply to the colon tissue leads to inflammatory damage known as ischemic colitis. This disease occurs eventually and starts when blood vessels become narrow and causes sudden abdominal pain together with cramping and bloody diarrhea. The development of ischemic colitis depends on elderly age and cardiovascular diseases and specific medications which negatively impact blood circulation. Treatment depends on the severity of the condition and can include antibiotic medications together with surgical procedures to remove affected colon parts[87].

Pseudomembranous Colitis:Pseudomembranous colitis is a condition in which the colon becomes inflamed, primarily due to an overgrowth of the bacterium clostridium difficile often triggered by antibiotics use that disturbs the natural balance of gut bacteria. Symptoms include severe diarrhea, abdominal pain & fever. The condition can lead to serious complications such as dehydration or colonic perforation if not treated. Treatment usually involves stopping the antibiotic that lead to the imbalance & starting targeted anti-microbial therapy such as vancomycin or fidaxomicin[88].

Pathophysiology of Ulcerative Colitis

Ulcerative colitis is a chronic disease characterized by diffuse mucosal inflammation limited to the colon. It involves the rectum in about 95% of cases and may extent proximally in a symmetrical, circumferential, and uninterrupted pattern to involve parts or all of the large intestine. The hallmark clinical symptom is bloody diarrhea often with prominent symptoms of rectal urgency and tenesmus. UC presents with damaged colonic mucin layers that cause the colon to develop higher mucosal permeability as well as pathogen invasion and misregulated immune cell activation patterns. When these events occur a combination of innate and adaptive immune system activation starts through Toll-like receptors combined with dendritic cells and T-cell imbalances affecting Th2 and NK-T cells thus activating pro-inflammatory cytokines TNF-α, IL-13, and IL-12/23 that cause epithelial apoptosis and leukocyte infiltration and develop chronic inflammation. The current therapeutic methods for IBD treatment combine anti-inflammatory 5-aminosalicylates (described by mesalamine), corticosteroids, immuno-suppressants (including azathioprine) with biologic medications (anti-TNF agents like infliximab) to maintain

remission control. Medical therapy now focuses on blocking particular cytokines or stopping leukocyte movements (anti-IL-12/23 and natalizumab constitute two examples of such therapies). Treatment options focus on disease severity levels from mild-moderate to moderate-severe and acute severe UC but remains restricted due to limited knowledge about the origin of UC and its varied disease course. [90,91].

Etiology

Ulcerative colitis is characterized as an ediopathic disease, however various possible etiologies have been proposed

- Infection
- Allergy to dietary components
- Immune response to bacterial
- Self-antigens and
- Environmental causes

Infectious causes include pathogenic microbial antigens triggers that have yet to be identified. However it appears to be more likely that normal intestine microflora as opposed to pathogenic organisms may have significant role in development of IBD. Defective Colonic mucosa and abnormal intestine epithelial permeability may increase the access of luminal dietary and bacterial products to the mucosa. [91]

Symptoms of ulcerative colitis

The first symptom is a progressive loosening of the feces. The patient may have crampy abdominal pain with sever urge to have a bowel movement. Diarrhea may begin slowly or suddenly. Symptoms may vary according to area of the colon which is affected and area inflamed. The most common symptoms include:

Abdominal pain, Bloody diarrhea with mucus

Fatigue(Tiredness)

Weight loss

Loss of appetite

Anemia

Elevated temperature

Dehydration

Tenesmus(Wanting to empty the bowels constantly) [91]

Classification of ulcerative colitis

Proctitis, Proctosigmoidsitis, Distal colitis, Extensive colitis and Pancolitis

Ulcerative proctitis- Ulcerative proctitismainly affects to the rectum. It is the mildest form of ulcerative colitis. Sign and Symptoms: Rectal bleeding, rectal pain, Feeling of urgency or inability to move the bowels even though there is an urge to do so. [89]

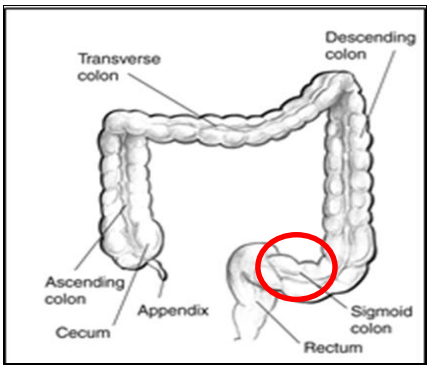

Fig No. 3: Ulcerative Proctitis.

Proctosigmoidsitis- Proctosigmoidsitis mainly affects the area which extends to the recto-sigmoid junction. (Lower end of colon). Signs and Symptoms include:Bloody diarrhea, Abdominal cramps, abdominal pain, Constant urge to go to the toilet.

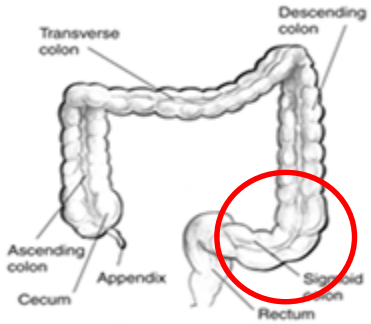

Fig No. 4: Proctosigmoidsitis.

Distal colitis- Distal colitis mainly affects the area which extends to the splenic flexure. Inflammation includes the rectum, up the left side through the sigmoid and descending colon.

Sign and symptoms include:Bloody diarrhea, Abdominal cramps on the left side, Weight loss.

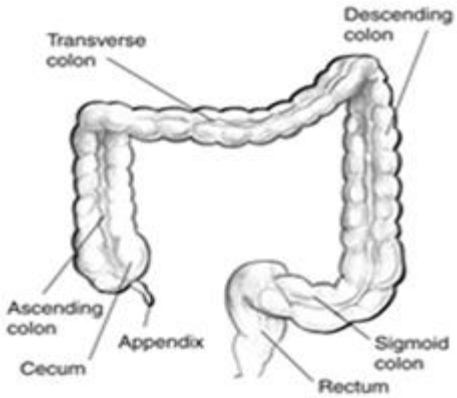

Fig no. 5: Distal colitis

Extensive colitis- Extensive colitis mainly extends to the hepatic flexure. Rare form of ulcerative colitis.

Signs and symptoms:Severe pain, Severe diarrhea, which leads to dehydration and shock.

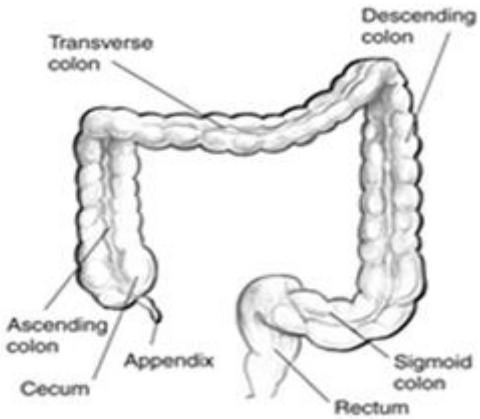

Fig No. 6 :Extensive colitis

Pancolitis-Pancolitismainly affects the area which extends from the rectum to the ceacum and involves the entite colon.

Signs and symptoms include: Bloody diarrhea, Abdominal cramps, Abdominal pain, Fatigue.

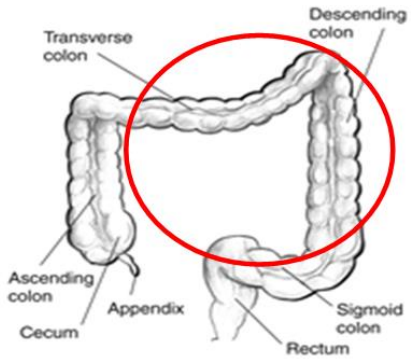

Fig No. 7:Pancolitis

Recent approaches and innovation for ulcerative colitis

Nanoparticles drug delivery system[37]. Enteric coated microneedle pills[35,36]. Size mediated targeting. [38]. Surface charge targeting[39,40]. Redox mediated targeting[41]. Ligand mediated targeting[42]. Lipid based vesicular delivery system [43,44,45]. Hybrid drug delivery system[49,50,51]. Pressure controlled drug delivery system. [53] Novel colon targeted drug delivery system (CODESTM)[54,55]. Osmotic controlled drug delivery (ORDS-CT) [56,57]. Pulsatile system (Pulsincap system). [61] Port system. [62] Mucoadhesive and penetrating novel drug delivery system. [64] Dual stimuli-responsive novel drug delivery system. [67,68,69]] Plant derived edible nano system. [70,71] Redox responsive novel drug delivery system. [28] Nano-in-Micro hybrid system (NPs-in-MPs). [75,76]]. 3D-Printed Personalized therapy. [78,79]. Microparticles. [80]

Microparticles for ulcerative colitis

Microparticles are also versatile in their applications. Microparticles are solid or liquid particles dimensionally ranging from 0.1um to 200um utilized extensively in the field of pharmaceutical drug delivery systems. They can be formulated for various routes of administration including oral, pulmonary, transdermal & intravenous delivery.

NEED OF MICROPARTICLES FOR ULCERATIVE COLITIS

The strategic delivery of drugs through microparticles permits direct treatment of inflamed parts in the colon which increases therapeutic outcomes. Monolithic distribution of drugs with microparticles leads to localized therapeutic activity and reduces systemic absorption together with related adverse effects which improves both comfort and security for patients. The gastrointestinal transit becomes better for sensitive therapeutics because the encapsulating microparticles improve their stability and solubility. The drug delivery mechanism controls medication release speed which produces extended therapeutic benefits while decreasing patients' need for multiple doses. The protection of drugs against breakdown coupled with precise delivery to action sites enables microparticles to enhance the availability of drugs with poor solubility. The design of microparticles systems depends on various polymers and carrier materials which allow developers to fulfill specific drug characteristics and release profile requirements. The formulation of microparticles enables storage of both hydrophilic and lipophilic drugs simultaneously in order to support a wide range of treatment needs for patients with ulcerative colitis. Other delivery methods such as pH-sensitive systems can be partnered with microparticles to create optimized drug release functions under gastrointestinal environments. The ability to transform microparticle delivery systems enables them to accommodate the pharmaceutical advancement of biologic compounds and genetically modified medications that need specific administration vehicles. Microparticles represent a potential method to deliver probiotics which restores the intestinal flora to aid ulcerative colitis management. [89]

METHODS OF PREPARATION

The therapeutic delivery method through microparticles helps to treat ulcerative colitis (UC) by targeting the inflammatory area specifically while reducing whole-body medical

side effects. Producers use different methods to create microparticles which require polymers together with other substances to encapsulate drugs.

Several established approaches exist for preparation purposes that include:

Solvent Evaporation. Spray Drying. Double Emulsion Solvent Evaporation. Coacervation. Electrostatic Assembly. Melt Dispersion. Supercritical Fluid Technology.

Spray Drying

A solution of the drug and polymer is sprayed into a hot gas stream, rapidly evaporating the solvent and forming dry microparticles. This method is having fast process, scalable, and suitable for heat-sensitive drugs. This helped in preparation of prednisolone-loaded microparticles for UC therapy. [98]

Procedure: The drug preparation starts by combining drug particles with polymer through solution or suspension methods that mix the drug in solvent together with the polymer. A spray dryer receives the solution to atomize it into droplets of small size. The hot air stream passes through the droplets to evaporate the solvent until only solid microparticles remain. At the base of the chamber rests the dried microparticles.

Solvent Evaporation

A polymer is dissolved in an organic solvent, and the drug is dissolved or suspended in the polymer solution. The solvent is then evaporated, forming solid microparticles. This method is simple, cost-effective, and able to encapsulate both hydrophilic and hydrophobic drugs. From this, preparation of mesalamine-loaded microparticles can be done for UC with high percentage of entrapment efficiency. [99]

Procedure

The preparation process starts with dissolving a polymer using dichloromethane or acetone as an organic solvent. The drug exists at two states during the process as it is either suspended or dissolved within the polymer solution. A solution containing the drug goes into a liquid phase which requires surfactants to maintain system stability. Application of reduced pressure or use of rotary evaporators enables the solvent to evaporate which results in the formation of solid microparticles. The collection process of microparticles happens through centrifugation together with filtration methods.

Double Emulsion Solvent Evaporation

This method involves the formation of a double emulsion (water/oil/water) containing the drug in the inner aqueous phase. The solvent is evaporated to form microparticles.By this method, high encapsulation efficiency for hydrophilic drugs can be achieved, followed by encapsulation of anti-inflammatory agents (e.g., budesonide) for UC. [100]

Procedure

An oil-in-water (O/W) emulsion is prepared by dissolving the drug and polymer in an organic solvent and emulsifying it in an aqueous phase. A second aqueous phase is added to create a double emulsion (water/oil/water, W/O/W). The solvent is evaporated under reduced pressure, forming solid microparticles. The microparticles are collected by centrifugation andwashed.

Coacervation

Phase separation is induced in a polymer solution, causing the polymer to coalesce into microparticles. The drug is then incorporated into this coacervate phase. This method is suitable for drugs with a high molecular weight. Coacervation of poly(lactic-co-glycolic acid) (PLGA) for UC drug delivery carried out in the studies.

Procedure

A polymer solution is prepared in a solvent. Coacervation is induced by adding a non-solvent (e.g., water or alcohol), causing the polymer to phase-separate from the solvent and form a polymer-rich phase. The drug is incorporated into the coacervate phase. The microparticles are solidified by further processing or solvent removal. [101]

Electrostatic Assembly

The drug is electrostatically bound to a polymer matrix, often using an electrostatic field to assemble the microparticles. High encapsulation efficiency and controlled release properties. Electrostatic assembly for the delivery of probiotics and anti-inflammatory agents for UC occurred followed by the method.

Procedure

A polymer solution containing the drug is prepared.

The drug-polymer solution is exposed to an electrostatic field, causing the charged particles to assemble into microparticles.

The solvent is evaporated, leaving behind solid microparticles.

The microparticles are collected and washed. [97]

Melt Dispersion

The drug and polymer are melted together and then cooled to form solidified microparticles. No solvents required, making it eco-friendly. This helped in preparation of melt-dispersion-based mesalamine microparticles for UC.

Procedure

The drug and polymer are heated until they melt and form a homogeneous melt. The molten mixture is cooled rapidly to form solidified microparticles. The microparticles are collected, usually by milling or sieving, to achieve the desired size. [102]

Supercritical Fluid Technology

Supercritical CO_2 is used to extract the solvent from a polymer-drug solution, creating microparticles. This method provides particles with narrow size distribution and high drug loading. Preparation of mesalamine or corticosteroid-loaded microparticles can be possible by this method.
Procedure:

A drug and polymer solution is prepared, usually in an organic solvent. The solution is mixed with supercritical CO_2 under high pressure. The CO_2 acts as a solvent for the polymer,and the solvent is evaporated as CO_2 diffuses out, leaving behind solid microparticles. The microparticles are collected after the CO_2 is vented off. [103]

Evaluation parameters for the microparticles

Particle Size and Distribution

Dynamic Light Scattering (DLS) is commonly employed to determine the size distribution of microparticles. A sample suspension is illuminated with a laser, and the scattered light is analyzed to calculate particle size based on Brownian motion.
Instruments used are Zetasizer Nano Series. [104]

Surface Morphology

Scanning Electron Microscopy (SEM) provides high-resolution images of the microparticle surface, allowing assessment of shape, surface texture, and uniformity. Samples are typically coated with a conductive layer to prevent charging.
Instruments used are JSM-6390LV. [95]

Entrapment Efficiency

The entrapment efficiency is determined by measuring the amount of drug encapsulated within the microparticles. Microparticles are dissolved, and the drug concentration is quantified using High-Performance Liquid Chromatography (HPLC).
Instruments used are Agilent 1260 Infinity II. [95]

Entrapment Efficiency (%)=Total amount of init ial loaded drug−Unentrapped drug
\Total amount of initial loaded drug ×100

In Vitro Drug Release

The release profile is evaluated by immersing microparticles in simulated gastrointestinal fluids at different pH levels to mimic the conditions of the stomach and colon. Samples are withdrawn at specified intervals, and drug concentration is measured. Instruments used are USP Apparatus II (paddle method). [95]

Zeta Potential

Zeta potential measurements assess the surface charge of microparticles, which influences stability and interaction with biological membranes. DLS can also provide zeta potential data. Instruments used are Zetasizer Nano Series. [95]

In Vivo Evaluation

Animal models, such as rats induced with colitis, are used to assess the therapeutic efficacy of microparticles. Parameters like histopathological changes, inflammatory cytokine levels, and clinical scores are evaluated. Instruments used are Histology: Olympus BX53. [95]

Stability Studies

Microparticles are stored under various conditions (e.g., different temperatures and humidity levels) to assess physical and chemical stability over time. Parameters such as drug content, particle size, and morphology are periodically evaluated.
Instruments used are HPLC: Agilent 1260 Infinity II. [95]

Ex Vivo Human Ulcerative Colitis Explant Model

Colonic biopsies are obtained from UC patients during endoscopic procedures. These tissue samples are cultured in specialized media to maintain their viability and inflammatory characteristics. Researchers then assess the secretion profiles of various cytokines and inflammatory markers to evaluate disease activity and response to treatments. Instruments used are Incubators for tissue culture, ELISA kits for cytokine quantification, and flow cytometers for cell analysis. [105]

Ex Vivo Organoid Models

Intestinal organoids are derived from UC patient biopsies and cultured in three-dimensional matrices. These organoids replicate the architecture and function of the human colon, providing a platform to study disease mechanisms and test drug responses. Instruments used are Bioreactors for Organoid culture, confocal microscopes for imaging, and qPCR machines for gene expression analysis. [106]

Ex Vivo Microfluidic Systems

Mouse colonic tissues are cultured in microfluidic devices that simulate the mechanical and chemical environment of the human colon. These systems allow for real-time monitoring of tissue responses to inflammatory stimuli and potential therapeutics. Instruments used are Microfluidic platforms, live-cell imaging systems, and automated fluid handling systems. [107]

Ex Vivo Drug Response Studies

UC patient-derived tissues are exposed to potential therapeutic agents. Researchers measure inflammatory cytokine levels, histological changes, and gene expression profiles to assess the efficacy of the treatments. Instruments used are High-performance liquid chromatography (HPLC) for drug quantification, immunohistochemistry for tissue analysis, and RT-PCR for gene expression studies. [108]

Future perspective

CTDDS represents an upcoming pharmaceutical innovation which elevates colonic drug delivery efficiency yet reduces adverse effects across the entire body. Microparticles show promise as a drug delivery method because they provide precise timed release capabilities and maintain stability inside the changing conditions of the colon. Future progress in this field depends on building "smart" microparticles from biodegradable, stimuli-responsive polymers including pectin, chitosan or Eudragit®. These materials respond to the colon's enzyme activity and neutral pH to provide drug delivery at exact locations. The drug delivery mechanism demands additional development since mucoadhesive additives would enable longer contact time between medicated particles and inflamed mucosal areas thereby boosting drug absorption through damaged tissues. As a new approach combination therapies encapsulate microparticles with anti-inflammatory agents and biologics or plant extracts or probiotics for parallel depression of inflammation alongside reestablishment of gut microbiome balance. Sensitivity of peptides and proteins will benefit from microparticles containing permeation enhancers and enzyme inhibitors that protect therapeutic agents against degradation and enhance their absorption throughout the colon. Tunable microparticles for individual treatment needs will be fundamental based on disease severity levels as well as pH conditions and microbial characteristics through new production methods of 3D-printed tablets with spatial drug release control. The essential base for these developments must consist of both scalable operations and environmental sustainability through low-cost production technologies like spray-drying or microfluidics and environmentally safe material selection of polymers. The combination of biological insights and material science with engineering principles enables microparticle-based CTDDS to revolutionize UC management by delivering safer and more effective therapies which lower the frequency of medication doses and decrease toxicity in systemic regions. These innovative concepts show promise for future treatment of UC and other colonic illnesses and promise new possibilities for biological drug delivery across the body because of their design for colon-specific targeting.

CONCLUSION

The article conducts a vital evaluation of upcoming colon drug delivery system technologies because they represent essential therapies for inflammatory bowel disease. The complete development of pharmaceutical

medicine requires deep knowledge of both colon bacterial functions and pH levels when developing useful products. Four distinct drug targeting approaches were evaluated through study using combinations of prodrugs with pH-responsive and time-based components and microbial-activated systems targeted for the colon area. The implementation of medical delivery systems achieves maximum drug effectiveness of insoluble agents while maintaining prominent concentrations but minimizing system-wide drug distribution. The report showcases promising results of biopolymer applications in formulation development while stability along with safety issues remains a challenge in the process. The newly developed therapeutic procedures work toward specific body areas to create promising medical breakthroughs which enhance patient care in colon-related conditions. Complete utilization of drug delivery methods for specific medical targets requires further investigation to make their implementation viable for healthcare services.

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