OPEN ACCESS

Saudi Journal of Medical and Pharmaceutical Sciences
Abbreviated Key Title: Saudi J Med Pharm Sci
ISSN 2413-4929 (Print) | ISSN 2413-4910 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Review Article **Pharmaceutics**

Management of Inflammatory Bowel Diseases: A Review

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DOI: 10.36348/sjmps.2022.v08i10.017 | **Received:** 15.09.2022 | **Accepted:** 21.10.2022 | **Published:** 30.10.2022

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Abstract

Inflammatory bowel diseases (IBD) are Ulcerative colitis (UC) and Crohn's disease (CD). Conventional therapies are inadequate and are associated with several systemic side effects due to lack to localization of active moiety at the inflamed site. Colonic drug targeting is a novel potentially active area of research intended and focused on drug delivery for treating localized disease. Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects.

Keywords: IBD, UC, CD, Colon drug delivery system.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic intestinal inflammatory [1] disorder with an unknown etiology. IBD is composed of two different disease entities: Crohn's disease (CD) and ulcerative colitis (UC). IBD has been thought to be idiopathic but has two main attributable causes that include genetic and environmental factors. The gastrointestinal tract in which this disease occurs is central to the immune system and the innate and the adaptive immune systems are balanced in complex interactions with intestinal microbes under homeostatic conditions. However, in IBD, this homeostasis is disrupted and uncontrolled intestinal inflammation is perpetuated. Recently, the pathogenesis of IBD has become better understood owing to advances in genetic and immunologic technology. Moreover, new therapeutic strategies are now being implemented that accurately targets the pathogenesis of IBD. Beyond conventional immune suppressive therapy, the development of biological agents that target specific disease [2] mechanisms has resulted in more frequent and deeper remission in IBD patients, with mucosal healing as a treatment goal of therapy. Future novel biologics should overcome the limitations of current therapies and ensure that individual patients can be treated with optimal drugs that are safe and precisely target IBD.

Crohn's Disease

Crohn's disease can affect any part of the GI tract, from the mouth to the anus. It most commonly affects the end of the small intestine (the ileum) where it joins the beginning of the colon. Crohn's disease may appear in ―patches,‖ affecting some areas of the GI tract while leaving other sections completely untouched. In Crohn's disease, the inflammation may extend through the entire thickness of the bowel wall.

Ulcerative Colitis

Ulcerative colitis is limited to the large intestine (colon) and the rectum. The inflammation occurs only in the innermost layer of the lining of the intestine. It usually begins in the rectum and lower colon, but may also spread continuously to involve the entire colon.

Symptoms of IBD

The symptoms of IBD vary from person to person, and may change over time. The most common symptoms for CD and UC are frequent and/or urgent bowel movements, diarrhea, bloody stool, abdominal pain and cramping. People with IBD may also report symptoms such as fatigue, lack of appetite and weight loss. IBD is characterized by times of active disease (flares), when symptoms are present, and times of remission, when little or no symptoms are present.

Causes

The exact cause of IBD remains unknown. Researchers believe that a combination of four factors lead to IBD: a genetic component, an environmental trigger, an imbalance of intestinal bacteria and an inappropriate reaction from the immune system. Immune cells normally protect the body from infection, but in people with IBD, the immune system mistakes harmless substances in the intestine for foreign substances and launches an attack, resulting in inflammation.

Diagnosis

The clinical presentations and symptoms of IBD are well described. It is not uncommon for patients with IBD to describe a long diagnostic process that can take months or years. The key to avoid such an event is to suspect IBD. Almost all patients with IBD have bowel symptoms [3-5], ie. Abdominal discomfort or pain and/or change of bowel habits (usually diarrhoea). The vast majority of patients with such symptoms however, will have irritable bowel syndrome (IBS) and require less aggressive investigation. The distinguishing features are alarm 'symptoms or signs, such as: rectal bleeding, weight loss, abdominal mass, fever, nocturnal symptoms etc.

IBD Complications

In addition to the signs and symptoms of IBD described on the preceding pages, some people develop complications that may require urgent medical care.

Complications of Ulcerative Colitis Include:

- ✓ Heavy, persistent diarrhea, rectal bleeding, and pain.
- ✓ Perforated bowel—chronic inflammation of the intestine may weaken the intestinal wall to such an extent that a hole develops.
- ✓ Toxic megacolon—severe inflammation that leads to rapid enlargement of the colon.

Complications of Crohn's Disease Include:

- ✓ Fistula—ulcers on the wall of the intestine that extend and cause a tunnel (fistula) to another part of the intestine, the skin or another organ.
- ✓ Stricture—anarrowing of asection of in testine caused by scarring, which can lead to an in testinal blockage.
- ✓ Abscess—acollection of pus, which can develop in the abdomen, pelvis, or around the analarea.
- ✓ Perforated bowel—chronic inflammation of the intestine may weaken the wall to such an extent that a hole develops.
- ✓ Malabsorption and malnutrition, including deficiency of vitamins and minerals.

Complications outside the GI Tract

Not all complications of IBD are confined to the GI tract. For reasons that are not entirely understood, some people develop symptoms that are related to the disease but affect other parts of the body. The most common of these complications affect the skin and bones. These extra intestinal complications may be evident in the eyes (redness, pain, and itchiness), mouth (sores), joints (swelling and pain), skin (tender bumps, painful ulcerations, and other sores/rashes), bones (osteoporosis), kidney (stones) and liver (primary sclerosing cholangitis, hepatitis, and cirrhosis)—occurs rarely.

Medical Treatment

There are five main categories of medications used to treat IBD:

- **Aminosalicylates:** These are anti-inflammatory compounds that contain 5-aminosalicylic acid (5-ASA). Examples are sulfasalazine, balsalazide, mesalamine, and olsalazine. These drugs (given orally or rectally) act to decrease inflammation at the wall of the intestine. They are used primarily to treat ulcerative colitis, both to reduce symptoms and maintain remission, but may not be as effective in treating Crohn's disease.
- **Corticosteroids:** These medications, which include prednisone, prednisolone, and budesonide, affect the body's ability to begin and maintain an inflammatory process. They keep the immune system in check. They are effective for short-term control of flare-ups. They are not recommended for long-term or maintenance use because of their side effects, which can include infection, bone loss, weight gain, cataracts, skin fragility, sleep disturbance, and mood swings.
- **Immunomodulators:** This class of medications modifies the activity of the immune system so that it cannot cause ongoing inflammation. Examples include azathioprine, 6- mercaptopurine (6- MP), and methotrexate. These drugs are generally used to maintain remission in people who have not responded to other medications or who have only responded tosteroids.
- **Antibiotics:** The antibiotics ciprofloxacin and metronidazole have modest benefit for people with Crohn's disease that affects the colon or the area around the anus. They may be used when infections, such as abscesses, occur. There is no substantial scientific evidence to support the use of antibiotics in the treatment of ulcerative colitis.
- **Biologic Therapies:** These are the most recently developed treatments for IBD. Biologic therapies are indicated for people with moderately to severely active disease who have not responded well to conventional therapy. Four of these agents (adalimumab, certolizumab pegol, golimumab and infliximab) target an inflammatory protein

called tumor necrosis factor (TNF). Natalizumab and vedolizumab work by blocking certain types of white blood cells from getting into in flamed tissues.

Surgical Treatment

Medication may not adequately control symptoms for everyone with IBD, and some people with these conditions develop complications that require surgery.

After 30 years of disease, up to a third of people with ulcerative colitis will require surgery. The standard surgical procedure for ulcerative colitis is removal of the colon and rectum. Most patients who have surgery for ulcerative colitis can have a procedure called an ileal pouch anal anastomosis (IPAA). In this procedure, after the entire colon and rectum is removed, the small intestine is attached to the anal area, creating a pouch to collect waste. This allows the patient to pass stool through the anus. Some patients who undergo this procedure develop complications, such as pouchitis (inflammation of the pouch). Some patients will need a permanent ileostomy, where the fecal waste empties into an external bag attached to the patient‘s abdomen.

About 70% of people with Crohn‘s disease eventually require surgery. Different types of surgical procedures may be performed for Crohn‘s disease, depending on the reason for surgery, severity of illness, and location of the disease in the intestines. Approximately 30% of patients who have surgery for Crohn‘s disease experience recurrence of their symptoms within three years and up to 60% will have recurrence within ten years.

Drug Delivery Strategies for Management of IBD

An ideal drug delivery system for IBD should release the drug at the affected site of gastrointestinal tract (GIT) preferably colon with localization and reduced dosing frequency. Moreover, it should delay the release of drug in order to achieve effective concentration required for local action

Conventional Targeting Strategies

Conventional strategies studied in the management of IBD rely on the controlled and sustained delivery systems. They basically take the advantage of the GIT physiology, particularly the colon [6]. The mechanism used in these delivery systems can be either based on chemical modification using the prodrug approach or those based on formulation i.e. i) coating with pH sensitive polymers, ii) Time Released systems, iii) Embedding in polysaccharide matrices and iv) Azopolymeric hydrogels.

Prodrug Approaches

Prodrug undergoes *in vivo* biotransformation and releases the drug at the desired site. The covalent linkage between the drug and carrier is acted upon by the colonic enzymes and drug is bioavailable (Figure 2). Various colonic enzymes are azoreductase, glycosidase, xylosidase and nitroreductase [7], etc. Robust and stable series of colon targeting compounds can be generated by conjugation of drugs with cyclodextrins, aminoacids, glucuronides etc. Covalent azo linkages between 5-amino Salicylates (5-ASA) and carrier molecules are most common prodrugs used in IBD. Similar more prodrugs used in management of IBD are cited in Table 1.

Table 1: Prodrug used in IBD

Type of conjugation	Drug (Trade Name)	Drug	Carriers	Active Bacterial Enzyme
Amino acid	5-ASA-Gly	5-ASA	Glycine	Peptidase
Azo linkages	Sulphasalazine	5-ASA	Sulphapyridine	Azoreductase
Dextrans	Dextrans-5-ASA	5-ASA	Dextrans	Azoreductase
Glucuronide	Glucu-Dex	Dexamethasone	$^{\beta}$D glucuronide	Glucuronidase

Coating with pH-Sensitive Polymers

The ileum and colon exhibit higher pH in the GIT. Dosage form that can disintegrate at this high pH ranges can be easily targeted to colon and latter part of ileum. Pharmaceutical industry has been using this technique to modify dosage forms by film coating capsules and tablets with pH - sensitive biocompatible polymers. Enteric coating films dissolve at intestinal pH and thus preserve the drug from the harsh acidic p H in stomach [8], acidic bile and microbial degradation. In the process, an extended and delayed release profile for the drug is observed such that it is released only in the intestinal area and increase therapeutic efficacy. Commonly used enteric polymers include derivatives of acrylic acids, co-polymers of methylacrylate (Eudragit) and cellulose polymers such as cellulose acetate trimellate and phthalate exhibiting a thresho ld pH in the range 4.5 -7.0. The system has also been extended for preparing nanoparticles, micro- particles and pellets. Subsequently these particles are filled in capsules. Such delivery systems thus improve the efficacy with site-specific drug release.

Time Dependent Release Systems

Time dependent release systems release drugs at predefined time at the desired site of GIT. This approach relies on the GI transit time from mouth to colon. Usually a lag time of 5 hours (h) is considered sufficient for colon delivery as the transit time for small intestine is about 34 h. The lag time is dependent upon the gastric motility [9] and size of dosage form. The dosage forms selectively releases the drug either by osmosis, swelling, or their combination and is unaffected by pH or microbial flora in the intestine.

Pulsincap® device is based on this approach. The device essentially has a non- disintegrating half capsule body. The open end of the capsule is locked with a hydrogel plug and then covered with the water-soluble capsule cap. The entire capsule is then coated with any enteric polymer. Enteric coating avoids premature release in case of variable gastric emptying. On reaching the intestine, the enteric coat dissolves and the hydrogel plug starts to swell. The quantity of hydrogel is adjusted in such a way that it pops out only after the stipulated period of time and the contents are released at specific site. In another similar approach, a hydrophobic material is coated upon the tablet with the surfactant. The hydrophobic admixture retains the capacity to rehydrate and re-disperse in aqueous environment in a time directly proportional tothe film thickness. Time clock containing diltiazem hydrochloride though not available commercially is a time dependent release mechanism with site specific delivery in inflamed ileum orcolon.

Embedding in Polysaccharide Matrices

Most of the polysaccharides are stable in presence of the GI enzymes. However, they are degraded in colon due to bacterial flora. Amylose, chitosan, chondroitin sulphate, cyclodextrins, dextrans, inulin, guar gum, pectin and locust bean gum, are among those polysaccharides known to be stable in proximal GIT, however degrades in distal GIT by colonic bacterial flora. The drug is thus released exclusively inthe colon. Derivatives of polysaccharides with improved properties, stability and bioadhesion are being used lately.

Azopolymeric Hydrogels

These pH- sensitive hydrogels contain acid side chains and azo aromatic cross-linker that are enzymatically degradable. At acidic pH, the hydrogels do not swell and hence exhibit minimum drug release. However, in intestinal pH the hydrogel swells with slow release of drug. Swelling of the hydrogels exposes the azo linkages to the enzymes. Cleavage of the azo bonds releases the drug in colon. Polyanionic hydrogels made of polyacrylic acids and linked with azo aromatic cross linkers have been studied for colon [11-14] targeting. These hydrogels yield minimum release of drug in the stomach. However in alkaline pH ionization of the carboxylic groups occurs and the hydrogel swells exposing the azo cross- links to azoreductase present in colon.

CODES™

CODESTM utilizes the combination of all approaches used in conventional targeting strategies i.e. pH, time and bacterial flora [15]. The system essentially consists of a trilayered coated tablet with core drug and biodegradable polysaccharides. The drug containing tablet core is coated with an acid soluble polymer, viz. Eudragit E. This is further coated with polysaccharide such as lactulose and subsequently coated with an enteric polymer Eudragit L. Eudragit L protects the tablet from stomach and immediately dissolves after gastric emptying. In colon region, the bacteria flora enzymatically degrades the polysaccharide (lactulose) into organic acid. This further lowers the pH and solubilizes acid soluble coating.

Pressure Controlled Drug Delivery System (PCDS)

PCDS is based on the fact that the luminal pressure in colon is higher than that found in small intestine. PCDS bears the luminal pressure found in small intestine but collapses in high colonic pressure. This results in drug release after 3-7 h of oral administration. PCDS are capsule shaped suppositories coated with water insoluble polymer ethyl cellulose. Upon oral administration, the suppository base liquefies and ethyl cellulose forms balloon. PCDS are not subjected to higher luminal pressure as sufficient fluid content [16-18] is available in proximal GIT. However, re- absorption of water in colon increases the viscosity of luminal contents resulting in increased intestinal pressure. The increased pressure and high-amplitude colonic peristalsis ruptures the PCDS and releases the drug in colon. Some of the products based on this mechanism are available commercially.

Osmotic Controlled Systems

This is a well-studied mechanism used for delayed or pulsed delivery. Osmotic gradient arises due to increased water diffusion [19] into osmotic layer. Drug and osmogen is directly compressed to form a core and this core is coated with a semipermeable membrane bearing a hole to permit the entry of intestinal fluid. This driving force results in release of drug through laser drilled holes. This system is essentially controlled by the water diffusion rate into the system and hence shows a constant zero order release. However the entire system (OROS-CT) is further coated with enteric coating so that drug is not released in upper GIT.

Multi-Particulate Drug Delivery System

Single-unit delivery systems face with varied challenges viz., unpredicted disintegration during GI transit with systemic side effects and reduced bioavailability at site of action. Systemic side effects of drugs used in IBD is of major concern [20]. Multi-particulate systems are known for controlled, sustained oral drug release with better chances of local targeting and increased stability in GI conditions due to encapsulation. Particulate delivery systems show higher adhesion at the site of inflammation due to increased mucus production, enhanced permeability due to disease state and particle uptake due to a number of immune cells. This phenomenon is found to be size dependent. Generally particles in the range of 5–15 μm have enhanced drug residence time in the colon with increased adhesion. While some reports state that micro- particles in the size range of 10– 300 μm target the inflamed tissue in IBD better. Encapsulation of drug

also prevents drug exposure to the P-glycoprotein efflux receptors and to mucosal metabolism usually Cytochrome P450 3A. These systems can also be combined with multiple approaches like pH and time. Local bioavailability of the drug thus increases. Multi-particulate systems thus perform better than single unit systems *in vivo* as they can easily spread along the length of the intestine. Thus multi-particulates result in less irritation and prolonged transit in the colon with reproducible release profile.

Redox Sensitive Polymer Coating

Inflamed tissues in case of IBD have higher levels of reactive oxygen species (ROS). Thus polymers containing thioketals sensitive to ROS can be used for coating dosage forms so that they get dissolved only in inflamed tissues. Upon oral administration the abnormal high levels of ROS will dissolve the polymer and provide site specific delivery [21, 22]. Increased uptake of redox nanoparticles was also observed in ROS treated epithelial colonic cells than those with reactive oxygen species untreated cells. Similar observation was seen in vivo inflamed colon in colitis induced mice model. Indirectly the ROS decreased and inflammation also subsided. The dose response efficacy ousted the positive control 5- ASA. In another example, redox nanoparticles with nitroxide radicals in the core revealed high accumulation in colonic mucosa and cancer tissues. Hence no toxicity was observed on long term oral administration in mice. Nitroxide radicals effectively scavenged ROS and suppressed tumor growth. Combination of redox nanoparticles with irinotecan further improved the therapeutic efficacy and suppressed the side effect.

PHLORAL

PHLORAL is a hybrid pH/microflora-activated technology [23] developed by some of the investigators who had previously developed COLAL, where it seeks to improve the consistency and accuracy of delivery, as well as assure rapid release of contained drug. COLAL relies on the controlled swelling of the amylose/ethylcellulose coating which can be a slow process resulting in a sustained-release mechanism that is not well-suited to fast release in the colon which leads to better targeting of the whole colon.

MMX® Technology

A combined delayed-release/ extended-release tablet technology [24] for the delivery of therapeutic agents to the whole colon has been developed, clinically validated in IBD and commercialised (for the glucocorticoid budesonide and the anti- inflammatory mesalazine). The technology is described as a multi-matrix structure, hence MMX. Tablets consist of a dispersion of drug- containing lipidic granules in a hydrophilic matrix coated with enteric acrylic copolymers. The coating delays the release until the tablet arrives at the intestine where the coating dissolves and the extended-release drug delivery begins. Release over the length of the colon allows for the topical application of the drug to the whole bowel surface affected by inflammation. The innovators of this technology have successfully demonstrated the efficacy of infliximab (anti- TNFα) delivered topically (as an enema) to a very small number of human subjects as treatment for IBD, and have completed an initial demonstration of the feasibility of incorporating the monoclonal antibody into MMX technology oral do sage forms.

CONCLUSION

The ever-increasing alarming rate of IBD needs development of new and sustained efforts in design of delivery approaches in IBD. Numerous issues such as stability in GIT, bio-distribution and reduced side-effects need to be addressed to prove their superiority over existing conventional therapies.

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