IJPSR (2021), Volume 12, Issue 7 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 11 May 2020; received in revised form, 12 December 2020; accepted, 16 May 2021; published 01 July 2021

A REVIEW ON INFLAMMATORY BOWEL DISEASE-RECENT PHARMACEUTICAL APPROACHES TO COMBAT IT

Nihar Ranjan Kar

Centurion University of Technology and Management, Rayagada - 765002, Odisha, India.

Keywords:

IBD, UC, CD,
Colon drug delivery system,
Side effects

Correspondence to Author:
Nihar Ranjan Kar

Assistant Professor,
Centurion University of Technology and Management, Rayagada - 765002, Odisha, India.

E-mail: nihar_795@rediffmail.com

ABSTRACT: Inflammatory bowel diseases (IBD) are chronic and relapsing intestinal inflammatory conditions, hallmarked by a disturbance in the bidirectional interaction between gut and brain. IBD is 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. Treatment option range from small molecules to macromolecules (peptides, proteins and oligonucleotides) that target multiple therapeutic pathways, and dosed *via* injectable, oral or the rectal route for local bowel treatment. Conventional therapies are inadequate and are associated with several systemic side effects due to a lack of localization of active moiety at the inflamed site. But 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.

INTRODUCTION: Inflammatory bowel disease (IBD) is a persistent intestinal inflammatory disease with an unknown etiology. IBD is composed of two specific disease entities: Crohn's disorder (CD) and ulcerative colitis (UC). IBD has been idea to be idiopathic however has two fundamental attributable causes that include genetic and environmental factors. The gastrointestinal tract in which this ailment takes place is imperative to the immune system, and the innate and adaptive immune systems are balanced in complicated interactions with intestinal microbes underneath homeostatic conditions [1].

QUICK RESPONSE CODE

DOI:
10.13040/IJPSR.0975-8232.12(7).3593-01

This article can be accessed online on
www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(7).3593-01

However, in IBD, this homeostasis is disrupted, and out-of-control intestinal infection is perpetuated. Recently, the pathogenesis of IBD has ended up better understood attributable to advances in genetic and immunologic technology. Moreover, new therapeutic techniques at the moment are being carried out that appropriately target the pathogenesis of IBD. Beyond conventional immune suppressive therapy, the development of organic agents that concentrate on precise disease 2 mechanisms has resulted in extra common and deeper remission in IBD patients, with mucosal healing as a remedy goal of therapy[2].

Crohn's Disease: Crohn's sickness can affect any part of the GI tract, from the mouth to the anus. It most typically impacts the end of the small intestine, where it joins the beginning of the colon. Crohn's disease may appear in patches affecting some areas of the GI tract at the same time as leaving other sections absolutely untouched. In

crohn ailment, the inflammation may increase through the entire thickness of the bowel wall [3].

Ulcerative Colitis: Ulcerative colitis is restrained to the big intestine (colon) and the rectum. The inflammation occurs best in the innermost layer of the lining of the intestine. It normally begins in the rectum and decreases colon; however, it might also spread continuously to contain the entire colon [4].

Symptoms of IBD: The signs of IBD range from individual to man or woman and may alternate over time. The most common signs and symptoms for CD and UC are common and/or pressing bowel movements, diarrhea, bloody stool, stomachache, and cramping. People with IBD may also file signs and symptoms inclusive of fatigue, lack of appetite, and weight loss. IBD is characterized by times of active disease (flares), while symptoms are present, and instances of remission, while little or no signs are present [5].

Causes: The exact cause of IBD stays unknown. Researchers accept as true that an aggregate of four factors causes IBD: a genetic component, an environmental trigger, an imbalance of intestinal bacteria, and a beside-the-point response from the immune device. Immune cells normally defend the frame from infection, but in people with IBD, the immune device mistakes innocent materials inside the gut for foreign materials and launches an attack, ensuing in inflammation [6]. ✓

Diagnosis: The clinical signs and symptoms of IBD are well described. It is not unusual for sufferers with IBD to describe a protracted diagnostic manner that can take months or years. The key to avoiding such an event is to suspect IBD. Almost all patients with IBD have bowel symptoms (3-5), *i.e.,* Stomach soreness or ache and/or trade of bowel habits (commonly diarrhoea). The substantial majority of patients with such signs and symptoms, however, could have irritable bowel syndrome (IBS) and require less aggressive investigation. The distinguishing features are alarm signs or signs, inclusive of rectal bleeding, weight loss, belly mass, fever, nocturnal signs, *etc.* [7]

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 [8].

Complications of Ulcerative Colitis Include: [9]

- Heavy, persistent diarrhoea, 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 mega colon-severe inflammation that leads to rapid enlargement of the colon

Complications of Crohn's Disease Includes: [10]

- 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 - an arrowing of a section of intestine caused by scarring, which can lead to an intestinal blockage.
- Abscess - a collection of pus, which can develop in the abdomen, pelvis, or around the anal area.
- 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: [11, 12]

- 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)

- 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 [13].

Corticosteroids: These medicinal drugs, which consist of prednisone, prednisolone, and budesonide, affect the body‘s capability to start and maintain an inflammatory process. They preserve the immune system in check. They are powerful for short-time period management of flare-ups. They are not advocated for long-time period, or protection use due to their facet effects, which can include infection, bone loss, weight gain, cataracts, skin fragility, sleep disturbance, and temper swings [14].

Immunomodulators: This magnificence of medi-cations modifies the interest of the immune system so that it can't purpose ongoing inflammation. Examples consist of azathioprine, 6- mercapto-purine (6- MP), and methotrexate. These capsules are usually used to maintain remission in people who've not answered to other medications or who have most effective spoke back to steroids [15].

Antibiotics: The antibiotics ciprofloxacin and metronidazole have modest benefits 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 [16].

Biological Therapies: These are the most recently developed treatments for IBD. Biological therapies are indicated for people with moderately to severely active disease who have not responded well to conventional therapy. Four of these agents (adalimumab, certolizumabpegol, 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 inflamed tissues [17].

Surgical Treatment: Medication might not correctly control symptoms for all people with IBD, and some human beings with these conditions develop headaches that require surgical operation. After 30 years of disease, up to a 3rd of humans with ulcerative colitis will require surgical operation. The standard surgical operation for ulcerative colitis is the elimination of the colon and rectum. Most patients who have surgical treatment for ulcerative colitis may have a technique known as an ileal pouch-anal anastomosis (IPAA) [18]. In this system, after the whole colon and rectum is removed, the small intestine is hooked up to the anal area, growing a pouch to gather waste. This allows the affected person to pass stool through the anus. Some sufferers who undergo this technique develop complications, along with pouchitis (irritation of the pouch). Some sufferers will want an everlasting ileostomy, in which the fecal waste empties into an external bag attached to the affected person‘s abdomen.

About 70% of human beings with Crohn‘s disease eventually require surgical treatment [19]. Different styles of surgical procedures can be performed for Crohn‘s disease, depending on the cause for surgical treatment, severity of illness, and vicinity of the disease in the intestines. Approximately 30% of sufferers who have a surgical operation for Crohn‘s disease experience recurrence of their signs within three years, and as much as 60% may have a recurrence within ten years [20].

Drug Delivery Strategies for Management of IBD: An ideal drug delivery system for IBD should release the drug at the affected site of the gastrointestinal tract (GIT), preferably the colon, with localization and reduced dosing frequency. Moreover, it should delay the release of the drug in order to achieve the effective concentration required for local action [21].

Conventional Targeting Strategies: [22] Conventional strategies studied in the management of IBD rely on the controlled and sustained delivery systems. They basically take advantage of the GIT physiology, particularly the colon. The mechanisms 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 poly-saccharide 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 the drug is bioavailable [23]. Various colonic enzymes are azoreductase, glycosidase, xylosidase, and nitroreductase, *etc*. Robust and stable series of colon targeting compounds can be generated by conjugation of drugs with cyclodextrins, amino acids, glucuronides, *etc*. Covalent azo linkages between 5- amino Salicylates (5-ASA) and carrier molecules are the most common prodrugs used in IBD [24]. Similar more prodrugs used in the 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	β D glucuronide	Glucuronidase

Coating with pH-sensitive Polymers: The ileum and colon exhibit higher pH in the GIT. Dosage form that can collapse at this excessive pH range can be easily centered to colon and latter part of the ileum. Pharmaceutical enterprise has been the usage of this method to regulate dosage paperwork by movie coating pills and capsules with pH touchy biocompatible polymers [25]. Enteric coating movies dissolve at intestinal pH and thus hold the drug from the tough acidic pH in stomach 8, acidic bile and microbial degradation. In the process, an prolonged and behind schedule launch profile for the drug is discovered such that it is released only in the intestinal area and increases healing efficacy [26]. Commonly used enteric® polymers include derivatives of acrylic acids, co-polymers of methylacrylate (Eudragit), and cellulose polymers together with cellulose acetate trimellate and phthalate displaying a threshold pH within the variety 4.5 -7.0. The gadget has also been prolonged for preparing nanoparticles, microparticles, and pellets. Subsequently, this debris are crammed in tablets. Such delivery systems thus improve the efficacy with site-unique drug release [27].

Time-Dependent Release Systems: Time-dependent launch systems launch pills at predefined time at the favored website of GIT. This technique is predicated on the GI transit time from mouth to colon. Usually, a lag time of 5 hours (h) is considered sufficient for colon delivery because the transit time for a small gut is set 34 h. The lag time relies upon the gastric motility and size of dosage form [28]. The dosage forms selectively release the drug either by using osmosis, swelling, or their combination and is unaffected via pH or microbial flora in the gut. Pulsincap® tool is primarily based on this approach [29]. The tool basically has a non-disintegrating half of the tablet body. The open quit of the tablet is locked with a hydrogel plug and then covered with the water-soluble pill cap. The whole pill is then lined with an enteric polymer. Enteric coating avoids premature release in case of variable gastric emptying. On attaining the intestine, the enteric coat dissolves, and the hydrogel plug starts to swell [30]. The quantity of hydrogel is adjusted in such a way that it pops out best after the stipulated period of time, and the contents are released at unique web site. In another similar method, a hydrophobic cloth is coated upon the pill with the surfactant [31]. The hydrophobic admixture retains the potential to rehydrate and re-disperse in aqueous environment in a time immediately proportional to the film thickness. Time clock containing diltiazem hydrochloride even though not available commercially, is a time-dependent launch mechanism with website online unique transport in inflamed ileum or colon [32].

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 [33]. 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

in the colon. Derivatives of polysaccharides with improved properties, stability, and bioadhesion are being used lately [34].

Azopolymeric Hydrogels: These pH-sensitive hydrogels contain acid side chains and azoaromatic cross-linker that are enzymatically degradable. At acidic pH, the hydrogels do not swell and hence exhibit minimum drug release [35]. However, in intestinal pH the hydrogel swells with slow release of the drug. The swelling of the hydrogels exposes the azolinkages to the enzymes. Cleavage of the azobonds releases the drug in colon. Polyanionic-hydrogels made of polyacrylic acids and linked with azo aromatic cross-linkers have been studied for colon targeting [36]. These hydrogels yield a 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 [37].

CODES™: CODES™ utilizes the combination of all approaches used in conventional targeting strategies *i.e.,* pH, time, and bacterial flora [38]. 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 [39]. This is further coated with a polysaccharide such as lactulose and subsequently coated with an enteric polymer Eudragit L. Eudragit L protects the tablet from the stomach and immediately dissolves after gastric emptying. In colon region, the bacteria flora enzymatically degrade the polysaccharide (lactulose) into organic acid. This further lowers the pH and solubilizes acid-soluble coating [40].

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 the small intestine but collapses in high colonic pressure [41]. 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 [42]. PCDS are not subjected to higher luminal pressure as sufficient fluid content 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 release the drug in colon. Some of the products based on this mechanism are available commercially [43].

Osmotic Controlled Systems: This is a well-studied mechanism used for delayed or pulsed delivery. Osmotic gradient arises due to increased water diffusion into the 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 [44]. This driving force results in the release of drugs 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 an enteric coating so that the drug is not released in upper GIT [45].

Multiparticulate Drug Delivery System: Single-unit delivery systems face varied challenges *viz*., unpredicted disintegration during GI transit with systemic side effects and a reduced bioavailability at the site of action. Systemic side effects of drugs used in IBD is of major concern [46]. Multiparticulate systems are known for controlled, sustained oral drug release with better chances of local targeting and increased stability in GI conditions due to encapsulation [47]. 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 [48]. While some reports state that microparticles in a size range of 10– 300 μm target the inflamed tissue in IBD better. Encapsulation of drugs also prevents drug exposure to the P-glycoprotein efflux receptors and to mucosal metabolism, usually Cytochrome P450 3A [49]. These systems can also be combined with multiple approaches like pH and time. Local bioavailability of the drug thus increases. Multiparticulate 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 [50].

Redox Sensitive Polymer Coating: Inflamed tissues in the 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 tissues51. Upon oral administration, the abnormally high levels of ROS will dissolve the polymer and provide site-specific delivery. Increased uptake of redox nanoparticles was also observed in ROS-treated epithelial colonic cells than those with reactive oxygen species untreated cells. A similar observation was seen *in-vivo* inflamed colon in colitis induced mice model [52]. 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 [53]. Hence no toxicity was observed on long-term oral administration in mice. Nitroxide radicals effectively scavenged ROS and suppressed tumor growth. A combination of redox nanoparticles with irinote can further improve the therapeutic efficacy and suppressed the side effects [54].

PHLORAL: PHLORAL is a hybrid pH/ microflora-activated technology 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 [55]. 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 [56]. PHLORAL aims to resolve these aspects by virtue of a pH and/ or microflora-triggered system as an a-fail safe targeting mechanism. It can be manufactured using conventional pharmaceutical manufacturing equipment and is being applied to several products currently in clinical trials, including an advanced stage trial of a product for the treatment of IBD [57]. PHLORAL uses methacrylic acid–methyl methacrylate co-polymer (1:2), Eudragit S™, as its pH-dependent soluble polymer, which starts to dissolve at pH 7.0, and it employs amylose or amylopectin as the microflora degraded polysaccharide. The mixed polymer/ polysaccharide film around a dosage form is applied using fluid bed coating from a solution/ dispersion prepared by mixing appropriate amounts of the amylose dispersion in an organic/aqueous solvent and the enteric polymer solution, to obtain a preferred polysaccharide: polymer ratio [58]. The optimum pH-dependent polymer: amylose ratio was found to be 7:3, which shows excellent resistance to in vitro drug release at pH 1.2 and pH 6.8 (for up to 12 h), but at pH 7.0 without enzymes or at pH 6.8 in the presence of α-amylase from Bacciluslicheni form, the drug release is initiated at around 3 h and is complete within 4-6 h [59]. PHLORAL has been verified as superior to purely pH-structured polymer systems in a have a look at in eight wholesome human topics [60]. Core tablets labeled with technetium-99m (99mTc, 4MBq) had been covered with the PHORAL coating and dosed in a randomized crossover protocol to the topics either fasted or fed (after a 392 kcal breakfast), or 30 minutes prior to the breakfast [61]. Following ordinary meal times, lunch four hours submit dose and dinner 9 h publish dose, the release of the radioactive label from the dosage shape changed into measured *in-vivo* through γ-scintigraphy. In all cases (no matter feeding status), the label was launched at the goal site, both at the ileocecal junction, the ascending colon, the transverse colon or at the splenicor hepatic flexures [62]. No dosage forms released any of the labels inside the belly or small intestine, and no dosage shape failed to launch the label *in-vivo*. This absolutely distinguishes this generation from the purely pH-dependent technologies generally used in setting up colon-centered therapies where, in some of the cases, dosage gadgets didn't release at al [l63].

MMX® Technology: A combined delayed-release/ extended-release tablet technology for the delivery of therapeutic agents to the whole colon has been developed, clinically validated in IBD and commercialized (for the glucocorticoid budesonide and the anti-inflammatory mesalazine) [64]. 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 [65]. Release

over the length of the colon allows for the topical application of the drug to the whole bowel surface affected by inflammation [66]. The tablet is made by combining drug, a lipophilic matrix-forming agent (for example, stearic acid, stearic acid/carnauba wax mixture or stearic acid/beeswax mixture), and an amphiphilic agent (for example, lecithin or diethylene glycol monomethyl ether), with a binder (low viscosity hydroxypropyl cellulose or povidone) to form granules [67]. These granules are blended with other non-functional excipients and the hydro-philic matrix-forming excipients (for example, hydroxypropyl cellulose, carbomer, alginate), and optionally additional active ingredient (dependent on dose and drug release profile desired), and tablets are compressed from this blend [68]. The tablets are then coated with enteric polymers, typically a mixture of methacrylic acid–methyl methacrylate copolymer (1:2) and methacrylic acid–methyl methacrylate copolymer (1:1) [69]. 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 a treatment for IBD, and have completed an initial demonstration of the feasibility of incorporating the monoclonal antibody into MMX technology oral dosage forms [70].

CONCLUSION: The ever-increasing alarming rate of IBD needs to develop new and sustained efforts in the 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.

ACKNOWLEDGEMENT: Declared none.

CONFLICTS OF INTEREST: The authors declare no conflict of interest, financial or otherwise.

REFERENCES:

1. Mamula P: Pediatric inflammatory bowel disease (2nd ed.), philadelphia: springer international publications 2017.
2. Kim, Hwan D and Jae C: Pathogenesis of Inflammatory Bowel Disease and Recent Advances in Biologic Therapies. Immune Network 2017; 17: 25.
3. Gomez J: Living with Crohn's disease. London, UK: Sheldon 2000.
4. Inflammatory Bowel Disease Nursing Manual. Germany: Springer International Publishing 2019.
5. Podolsky DK: Inflammatory Bowel Disease. N Engl J Med 2002; 347: 417-29.
6. Yue B, Luo X, Yu Z, Mani S, Wang Z and Dou W: Inflammatory Bowel Disease: A Potential Result from the Collusion between Gut Microbiota and Mucosal Immune System. Microorganisms 2019; 7(10): 440.
7. Pediatric Inflammatory Bowel Disease. Netherlands: Springer New York 2012.
8. Hua S, Marks E, Schneider JJ and Keely S: Advances in oral nano-delivery systems for colon targeted drug delivery in inflammatory bowel disease: Selective targeting to diseased versus healthy tissue. Nanomedicine. 2015; 11: 1117-32.
9. Fakhoury M, Negrulj R, Mooranian A and Al-Salami H: Inflammatory bowel disease: clinical aspects and treatments. J Inflamm Res 2014; 7: 113-20.
10. Triantafillidis JK, Merikas E and Georgopoulos F: Current and emerging drugs for the treatment of inflammatory bowel disease. Drug Des Devel Ther. 2011; 5: 185-210.
11. Devlin SM and Panaccione R: Evolving inflammatory bowel disease treatment paradigms: top-down versus step-up. Med Clin North Am 2010; 94: 1-18.
12. Langholz E, Munkholm P, Davidsen M and Binder V: Course of ulcerative colitis: analysis of changes in disease activity over years. Gastroenterology 1994; 107: 3-11.
13. Lapidus A, Bernell O, Hellers G and Lofberg R: Clinical course of colorectal Crohn‘s disease: a 35-year follow-up study of 507 patients. Gastroenterol 1998; 114: 1151- 60.
14. Ephgrave K: Extraintestinal manifestations of Crohn’s disease. Surg Clin North Am 2007; 87(3): 673-80.
15. Duricova D, Pedersen N and Elkjaer M: Overall and cause-specific mortality in Crohn’s disease: a meta-analysis of population-based studies. Inflamm Bowel Dis 2010; 16: 347-53.
16. Jess T, Gamborg M, Munkholm P and Sørensen TIA: Overall and cause-specific mortality in ulcerative colitis: meta-analysis of population-based inception cohort studies. Am J Gastroenterol 2007; 102: 609-17.
17. Russell RK and Satsangi J: Does IBD run in families? Inflamm Bowel Dis 2008; 14(S2): S20-S21.
18. Noble CL and Arnott IDR: What is the risk that a child will develop inflammatory bowel disease if one or both parents have IBD? Inflamm Bowel Dis 2008; 14(S2): S22-S23.
19. Bennett RA, Rubin PH and Present DH: Frequency of inflammatory bowel disease in offspring of couples both presenting with inflammatory bowel disease. Gastroenterology 1991; 100: 1638-43.
20. Noomen CG, Hommes DW and Fidder HH: Update on genetics in inflammatory disease. Best PractRes Clin Gastroenterol 2009; 23(2): 233-43.
21. Loftus EV: Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology 2004; 126(6): 1504-17.
22. Bernstein CN: Assessing environmental risk factors affecting the inflammatory bowel diseases: a joint workshop of the Crohn‘s& Colitis Foundations of Canada and the USA. Inflamm Bowel Dis 2008; 14(8): 1139-46.
23. Cosnes J: What is the link between the use of tobacco and IBD? Inflamm Bowel Dis 2008; 14 (Suppl2): S14-S5.
24. Loftus EV, Shivashankar R, Tremaine WJ, Harmsen WS and Zinsmeiseter AR: Updated Incidence and Prevalence of Crohn‘s Disease and Ulcerative Colitis in Olmsted County, Minnesota (1970-2011). ACG 2014 Annual Scientific Meeting. October 2014.

25. Sewell JL, Inadomi JM and Yee HF: Race and inflammatory bowel disease in an urban healthcare system. Dig Dis Sci 2010; 55: 3479-87.
26. Probert CS, Jayanthi V, Pinder D, Wicks AC and Mayberry JF: Epidemiological study of ulcerative proctocolitisin Indian migrants and the indigenous population of Leicestershire. Gut 1992; 33: 687-93.
27. Nguyen GC, Torres EA and Regueiro M: Inflammatory bowel disease characteristics among African Americans, Hispanics, and non-Hispanic whites: characterization of a large North American cohort. Am J Gastroenterol 2006; 101(5): 1012-23.
28. Kappelman MD, Moore KR, Allen JK and Cook SF: Recent trends in the prevalence of Crohn's disease and ulcerative colitis in a commercially insured US population. Dig Dis Sci 2013; 58: 519-25.
29. Shahiwala A and Misra A: Novel Drug Delivery Technologies: Innovative Strategies for Drug Re-positioning. Germany: Springer 2019.
30. Bruschi ML: Strategies to modify the drug release from pharmaceutical systems. Amsterdam: Elsevier/Woodhead Publishing 2017.
31. Netherlands S: Surface Coatings: Vol I-Raw Materials and Their Usage (Vol. I). Dordrecht: Springer Netherlands 2013.
32. Kaplan D: Biopolymers from renewable resources. Berlin: Springer 2011.
33. Food and Drug Administration. Ulcerative Colitis: Clinical Trial Endpoints. August 2016: 1-19.
34. Lloyd-Price J, Arze C, Ananthakrishnan AN, Schirmer M, Avila-Pacheco J, Poon TW, Andrews E, Ajami NJ, Bonham KS, Brislawn CJ, Casero D, Courtney H, Gonzalez A, Graeber TG, Hall AB, Lake K, Landers CJ, Mallick H, Plichta DR and Huttenhower C: Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases. Nature 2019; 569(7758): 655-62.
35. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, Hayee B, Lomer MCE, Parkes GC, Selinger C, Barrett KJ, Davies RJ, Bennett C, Gittens S, Dunlop MG, Faiz O, Fraser A, Garrick V, Johnston PD and Hawthorne AB: British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut 2019; 68: s1–s106.
36. Alatab S, Sepanlou SG, Ikuta K, Vahedi H, Bisignano C, Safiri S, Sadeghi A, Nixon MR, Abdoli A, Abolhassani H, Alipour V, Almadi MAH, Almasi-Hashiani A, Anushiravani A, Arabloo J, Atique S, Awasthi A, Badawi A, Baig AAA and Naghavi M: The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet Gastroenterology and Hepatology 2020; 5(1): 17-30.
37. Papamichael K, Cheifetz AS, Melmed GY, Irving PM, Vande-Casteele N, Kozuch PL, Raffals LE, Baidoo L, Bressler B, Devlin SM, Jones J, Kaplan GG, Sparrow MP, Velayos FS, Ullman T and Siegel CA: Appropriate therapeutic drug monitoring of biologic agents for patients with inflammatory bowel diseases. Clinical Gastroenterology and Hepatology 2019; 17(9): 1655-68.
38. Reinisch W, Reinink AR and Higgins PDR: Factors associated with poor outcomes in adults with newly diagnosed ulcerative colitis. Clinical Gastroenterology and Hepatology 2015; 13(4): 635-42.
39. Mahadevan U, Robinson C, Bernasko N, Boland B, Chambers C, Dubinsky M, Friedman S, Kane S, Manthey J, Sauberan J, Stone J and Jain R: Inflammatory bowel disease in pregnancy clinical care pathway: a report from the american gastroenterological association ibd parenthood project working group. Gastroenterology, 2019; 156(5): 1508-24.
40. Leitner GC: Pharmacological- and non-pharmacological therapeutic approaches in inflammatory bowel disease in adults. World Journal of Gastrointestinal Pharmacology and Therapeutics 2016; 7(1): 5.
41. Colombel JF, D'Haens G, Lee WJ, Petersson J and Panaccione R: Outcomes and Strategies to Support a Treat-to-target Approach in Inflammatory Bowel Disease: A Systematic Review. Journal of Crohn's and Colitis 2020; 14(2): 254-66.
42. Yeshi K, Ruscher R, Hunter L, Daly NL, Loukas A and Wangchuk P: Revisiting inflammatory bowel disease: pathology, treatments, challenges and emerging therapeutics including drug leads from natural products. Journal of Clinical Medicine 2020; 9(5): 1273.
43. Ooi CJ, Hilmi I, Banerjee R, Chuah SW, Ng SC, Wei SC, Makharia GK, Pisespongsa P, Chen MH, Ran ZH, Ye BD, Park DI, Ling KL, Ong D, Ahuja V, Goh KL, Sollano J, Lim WC, Leung WK and Leong RWL: Best practices on immunomodulators and biologic agents for ulcerative colitis and Crohn's disease in Asia. Journal of Gastroenterology and Hepatology (Australia) 2019; 34(8): 1296-1315.
44. Weatherspoon D: Inflammatory Bowel Disease: Types, Causes, and Risk Factors. https://www.healthline.com/health/inflammatory-bowel-disease#causes
45. Talley NJ, Abreu MT, Achkar JP, Bernstein CN, Dubinsky MC, Hanauer SB, Kane SV, Sandborn WJ, Ullman TA and Moayyedi P: An evidence-based systematic review on medical therapies for inflammatory bowel disease. American Journal of Gastroenterology 2011; 106(SUPPL. 1): S2-S31.
46. Pagnini C, Pizarro TT and Cominelli F: Novel pharmacological therapy in inflammatory bowel diseases: Beyond anti-tumor necrosis factor. Frontiers in Pharmacology 2019; 10(JUN): 1-11.
47. Bischoff SC, Escher J, Hébuterne X, Kłęk S, Krznaric Z, Schneider S, Shamir R, Stardelova K, Wierdsma N, Wiskin AE and Forbes A: ESPEN practical guideline: Clinical Nutrition in inflammatory bowel disease. Clinical Nutrition 2020; 39(3): 632-53.
48. Feakins RM: Inflammatory bowel disease biopsies: Updated British Society of Gastroenterology reporting guidelines. J of Clinical Pathology 2013; 66(12): 1005-26.
49. Hazel K and O'Connor A: Emerging treatments for inflammatory bowel disease. Therapeutic Advances in Chronic Disease 2020; 11: 1-12.
50. Sulz MC, Burri E, Michetti P, Rogler G, Peyrin-Biroulet L and Seibold F: Treatment Algorithms for Crohn's Disease. Digestion 2020; 101(Suppl1): 43-57.
51. Danese S, Allez M, Van Bodegraven AA, Dotan I, Gisbert, JP, Hart A, Lakatos PL, Magro F, Peyrin-Biroulet L, Schreiber S, Tarabar D, Vavricka S, Halfvarson J and Vermeire S: Unmet Medical Needs in Ulcerative Colitis: An Expert Group Consensus. Digestive Diseases 2019; 37(4): 266-83.
52. De Mattos BRR, Garcia MPG, Nogueira JB., Paiatto LN, Albuquerque CG, Souza, CL, Fernandes LGR, Tamashiro WMDSC and Simioni PU: Inflammatory bowel disease: An overview of immune mechanisms and biological treatments. Mediators of Inflammation 2015. https://doi.org/10.1155/2015/493012
53. Suarez-Cortina, L, Perdomo-Giraldi M and Escobar-Castro H: Inflammatory bowel disease. Anales Espanoles de Pediatria 1993; 39(3): 185-89.

54. Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, Mitton S, Orchard T, Rutter M, Younge L, Lees C, Ho GT, Satsangi J and Bloom S: Guidelines for the management of inflammatory bowel disease in adults. Gut 2011; 60(5): 571-607.
55. Kondamudi PK, Malayandi R, Eaga C and Aggarwal D: Drugs as causative agents and therapeutic agents in inflammatory bowel disease. Acta Pharmaceutica Sinica B, 2013; 3(5): 289-96.
56. Miligkos M, Papamichael K and Vande-Casteele N: Efficacy and safety profile of anti-tumor necrosis factor-a versus anti- integrin agents for the treatment of Crohn's disease: a network meta-analysis of indirect comparisons. Clin Ther 2016; 38: 1342-58.
57. Katsanos KH, Papamichael K and Feuerstein JD: Biological therapies in inflammatory bowel disease: beyond anti-TNF therapies. Clin Immunol 2018 Mar 12 [Epub ahead of print].
58. Ben-Horin S and Chowers Y: Loss of response to anti-TNF treatments in Crohn's disease. Aliment Pharmacol Ther 2011; 33: 987-95.
59. Papamichael K, Vande Casteele N and Ferrante M: Therapeutic drug monitoring during induction of anti-tumor necrosis factor therapy in inflammatory bowel disease: defining a thera- peutic drug window. Inflamm Bowel Dis 2017; 23: 1510-15.
60. Papamichael K, Gils A and Rutgeerts P: Role for therapeutic drug monitoring during induction therapy with TNF antagonists in IBD: evolution in the definition and management of primary nonresponse. Inflamm Bowel Dis 2015; 21: 182-97.
61. Papamichael K and Cheifetz AS: Use of anti-TNF drug levels to optimise patient management. Frontline Gastroenterol 2016; 7: 289-300.
62. Barclay ML, Karim S and Helms ETJ: Infliximab and adalimu- mab concentrations and anti-drug antibodies in inflammatory bowel disease control using New Zealand assays. Intern Med J 2019; 49: 513-18.
63. Roblin X, Rinaudo M and Tedesco E: Development of an algo- rithm incorporating pharmacokinetics of adalimumab in inflam- matory bowel diseases. Am J Gastroenterol 2014; 109: 1250-56.
64. Roblin X, Marotte H and Rinaudo M: Association between pharmacokinetics of adalimumab and mucosal healing in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol 2014; 12: 80-84.
65. Yanai H, Lichtenstein L and Assa A: Levels of drug and anti- drug antibodies are associated with outcome of interventions after loss of response to infliximab or adalimumab. Clin Gastroenterol Hepatol 2015; 13: 522-30.
66. Yarur AJ, Jain A and Hauenstein SI: Higher adalimumab levels are associated with histologic and endoscopic remission in patients with Crohn's disease and ulcerative colitis. Inflamm Bowel Dis 2016; 22: 409-15.
67. Ungar B, Levy I and Yavne Y: Optimizing anti-TNF-a therapy: serum levels of infliximab and adalimumab are associated with mucosal healing in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol 2016; 14: 550-57.
68. Frederiksen MT, Ainsworth MA and Brynskov J: Antibodies against infliximab are associated with de novo development of antibodies to adalimumab and therapeutic failure in infliximab- to-adalimumab switchers with IBD. Inflamm Bowel Dis 2014; 20: 1714-21.
69. Mazor Y, Almog R and Kopylov U: Adalimumab drug and antibody levels as predictors of clinical and laboratory response in patients with Crohn's disease. Aliment Pharmacol Ther 2014; 40: 620-28.
70. Imaeda H, Takahashi K and Fujimoto T: Clinical utility of newly developed immunoassays for serum concentrations of adali- mumab and anti-adalimumab antibodies in patients with Crohn's disease. J Gast 2014; 49: 100-09.

How to cite this article:
Kar NR: A review on inflammatory bowel disease-recent pharmaceutical approaches to combat it. Int J Pharm Sci & Res 2021; 12(7): 3593-01. doi: 10.13040/IJPSR.0975-8232.12(7).3593-01.