MULTI-PARTICULATE MESALAMINE USED IN THE MANAGEMENT OF IBD: A REVIEW

Meenakshi Jaiswal*
Assistant Professor, Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University) Bilaspur, 495009, India

***Corresponding author: Meenakshi Jaiswal**,
Assistant Professor, Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University) Bilaspur, 495009, India; Email: meenakshi_123123@rediffmail.com, Mobile:09770166557

ABSTRACT

Crohn's disease and ulcerative colitis are examples of inflammatory bowel disease, which is a group of diseases that cause persistent inflammation of the digestive tract. These illnesses are now major public health concerns. With the development of targeted biologic therapies, the improvement of older therapies like immunomodulators and 5-aminosalicylic acid, and a deeper understanding of the mucosal immune system and the genetics involved in the pathogenesis of IBD, medical therapy for IBD has advanced dramatically in the last decade. Inflammatory bowel disease treatment aims to achieve and sustain remission. The standard practice in medicine nowadays is to start with less intense treatments and work our way up to more intense ones if those fail or if the patient reports that their illness is particularly aggressive. For this reason, multi-unit carriers are preferable over single-unit ones. Pectin, among other biopolymers, stands out as a promising option for building colon-specific carriers that are activated by microbes. In this article, we will discuss the current methods of managing inflammatory bowel illness with multi particle medication delivery.

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are two examples of IBDs; both are chronic inflammatory disorders of the gastrointestinal tract that cause recurrent ulceration of the colon. Diarrhea, abdominal pain, bleeding, anemia, and weight loss are just some of the serious symptoms of irritable bowel syndrome (IBS). Arthritis, ankylosing spondylitis, sclerosing cholangitis, and uveitis, iritis, and pyoderma gangrenosum and erythema nodosum are just some of the extra intestinal symptoms linked to this condition [1, 2]. It is believed that genetic, environmental, and immunological variables all play roles in the etiology of IBD. Noncaseous epithelioid granulomas in the intestinal mucosa are primarily macrophage-mediated. When macrophages are activated, they release cytokines such tumor necrosis factor- (TNF-) and interleukins. Rather than changing or reversing the underlying pathogenic mechanism, current medication treatments try to induce and sustain the patient in remission and relieve the disease's secondary consequences [3]. Regularly prescribed medications include corticosteroids, aminosalicylates, and immunosuppressive drugs such azathioprine. Alternative treatments include medications like metronidazole and broad-spectrum antibiotics, as well as cholestyramine, sodium cromoglycate, bismuth and arsenical salts, methotrexate, and fish oils. Humanized monoclonal antibody compositions have shown promise as a new method for treating

inflammatory bowel disease (IBD) [4], with the potential to replace established therapies by modulating the biochemical inflammatory pathways that are disrupted by the disease. In inflammatory bowel disease, the goals of pharmacotherapy include preventing and treating flare-ups, keeping patients in remission, and managing complications including fistulas. Some medications may work better than others for achieving these goals. Steroids, for instance, are the therapy of choice for moderate to severe flare-ups, but their long-term usage is discouraged due to their adverse effects and failure to maintain remission [5]. Other immunosuppressants, such as azathioprine, are recommended for long-term therapy but have a limited use in the acute setting since their therapeutic effect takes several weeks to develop. Biological therapies that can target individual steps in the immune cascade have been developed as our understanding of the inflammatory response has increased and our biotechnology has advanced. It has also been difficult to get drugs to the right place in the digestive tract, which is why newer, more effective drugs with less negative side effects are being developed as part of a "second-generation" effort [6, 7].

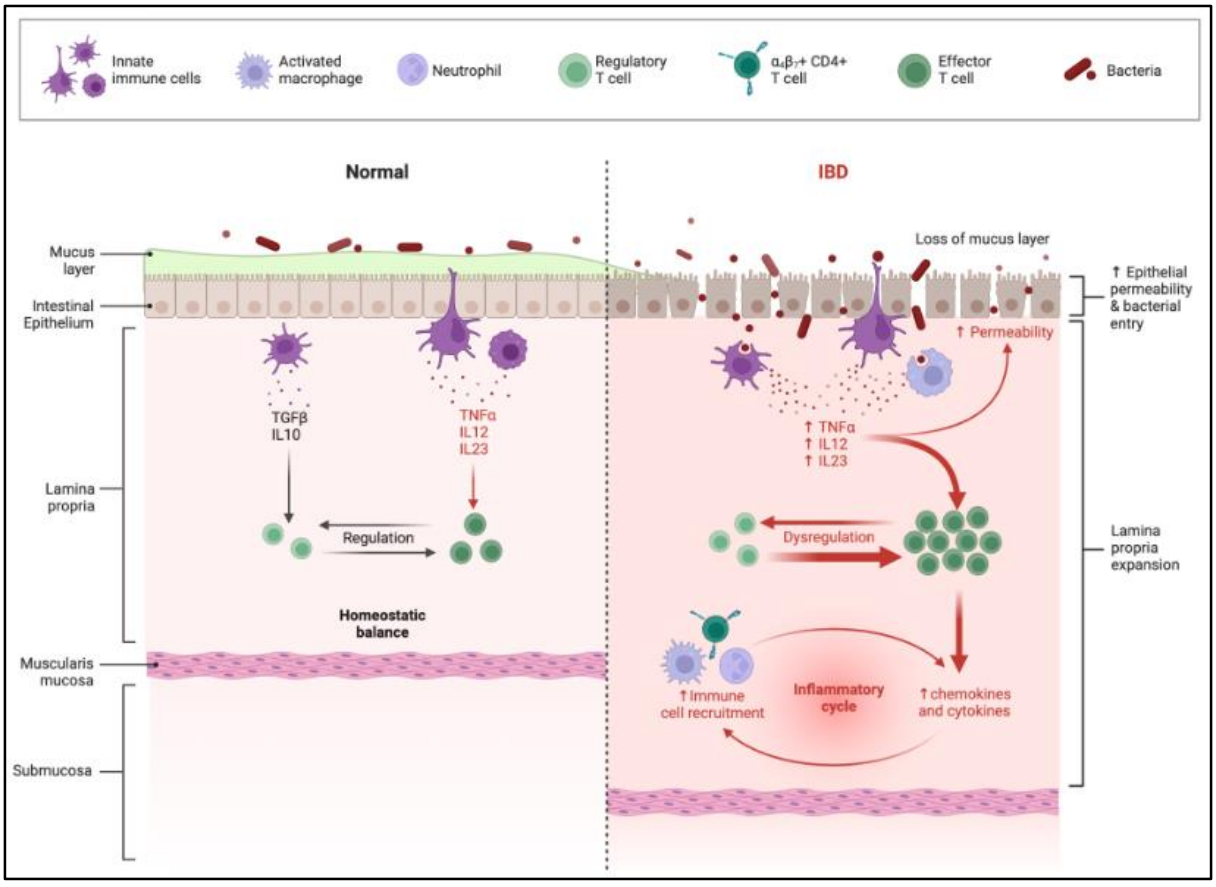

Figure 1: Immunological response in IBD

Metabolic pharmacokinetics Mesalamine is a 5-aminolevulinic acid molecule used for UC induction and maintenance treatment. It has been used to treat ulcerative colitis since the 1940s after its discovery as the active anti-inflammatory component of sulfasalazine. Bacterial azoreductase in the small intestine and colon liberates mesalamine from the sulfasalazine's azo bond to sulfapyridine [8]. The inert sulfapyridine is largely responsible for the hypersensitivity reactions and side effects of sulfasalazine; it is absorbed in the colon. Thirty percent of the free 5-ASA is promptly absorbed in the small intestine, and the enzyme N-acetyltransferase 1 in the intestinal epithelial cells and the liver converts it to N-Ac-5ASA. Both free 5-ASA and N-Ac-5-ASA are then urinated out. It's important to

emphasize that majority of the participants in these trials were healthy adults, while both inactive and active UC patients were included as well. Because inflammation can slow down GI motility and transit, the pharmacokinetics described above may not apply to the context of active colitis [9, 10].

Spondylarthritis, peripheral arthritis, cutaneous signs, ocular inflammation, primary sclerosing cholangitis, and hypercoagulability are extraintestinal symptoms of CD that are caused by intestinal inflammation. Malabsorption-related complications can further add to the difficulty of living with CD. Long-term CD can be worsened by gastrointestinal adenocarcinoma, which has received more attention as of late [11, 12]. Intestinal obstruction, inflammatory mass, or abscess are common complications that arise when the ilium or colon is afflicted. Acute ileitis symptoms can be mistaken for those of appendicitis, and in extremely rare cases, Crohn's disease is confined to the appendix. Perianal manifestations are distinctive to CD and may precede the development of gastrointestinal symptoms, in contrast to ulcerative colitis. Rectal hemorrhage, perianal complications, and skin and joint complications are common complaints in patients with CD that is confined to the colon. When Crohn's disease is confined to the colon, distinguishing it from ulcerative colitis can be challenging. Multiple stenosis, bacterial overgrowth, and protein-losing enteropathy are uncommon but common complications of the rare form of jejunoileitis known as diffuse jejunoileitis [13].

Are multiple-particulate carriers superior to single-particulate carriers?

The researchers have developed colon-specific dosage forms that are both single-unit and multiple-unit in order to achieve colon-specific medication release. However, compared to single-unit carriers, multiple-unit carriers offer a number of benefits that cannot be ignored. In comparison to single-unit dosage forms, multiple-unit dosage forms typically display consistent drug absorption because of their ability to be uniformly spread throughout the large intestine [13-15].

Multiple-particulate system

Oral dosage forms make up the majority of multi-particulate drug delivery systems. These dosage forms are composed of a multitude of small discrete units, each of which possesses some features that are sought. The dosage of the pharmacological ingredients is often divided on a plurality of subunits inside these systems. These subunits typically consist of thousands of spherical particles with diameters ranging from 0.05 to 2.00 millimeters. Therefore, multiparticulate dose forms are pharmacological formulations in which the active component is present as a number of small independent subunits. Multiparticulate dosage forms are also known as MPDFs [16, 17]. These subunits are then placed inside of a sachet before being encapsulated or crushed into a tablet in order to deliver the whole dose that is recommended. Multiparticulates are distinct particles that make up a multiple unit system. Due to the fact that they only consist of one unit, they offer numerous advantages over single-unit systems. Because multiparticulates are less dependent on stomach emptying, there is less inter- and intra-subject variability in the length of time it takes for them to move through the digestive tract [18]. They also have a better distribution and are less likely to cause irritation in the local area. In recent years, a significant amount of focus has been placed on the development of multiparticulate dosage forms rather than single unit delivery systems. This is due to the potential benefits of multiparticulate dosage forms, which include enhanced bioavailability, decreased risk of systemic toxicity, decreased risk of local irritation, and predictable gastric emptying [19].

Formulating a drug as a multiparticulate system can be done for many different reasons. One of these reasons is to assist the drug's disintegration in the stomach. Another reason is to produce a handy, quickly disintegrating tablet that dissolves in water before being swallowed [20]. This can help older patients and youngsters comply with their medication regimens. Conventional formulations are shown to be less

reproducible in terms of pharmacokinetic behavior compared to multiparticulate systems. After the disintegration, which takes place within a few minutes and sometimes even within seconds, the individual subunit particles move through the gastrointestinal tract at a rapid rate. If the diameter of these subunits is less than 2 millimeters, they are able to pass through the pylorus and out of the stomach continually, even while the pylorus is closed. As a consequence, there is less variation in plasma levels and bioavailability within and between individuals as a result of this [21-23].

Multiple-Particulate Carriers in IBD

The coating, gastric emptying, transit time in the small intestine, intraluminal pH, and coating all play a role in how much mesalamine is delivered to the colon. When pure mesalamine is ingested orally, it is rapidly absorbed in the proximal gastrointestinal system, where it is then acetylated and excreted in the urine and feces [24, 25]. Because the pharmacological effects of mesalamine in UC are dependent on topical contact with the colonic mucosa, successful transport of mesalamine to the colon is dependent on preventing its absorption in the proximal gastrointestinal tract. Medication containing 5-ASA comes in a number of different formulations, and these formulations can be distinguished from one another according to the method by which they postpone the release of mesalamine until it reaches the colon. Because there is a rising pH gradient from the proximal to the distal intestinal tract, certain delivery methods feature an enteric coating that dissolves when the pH goes beyond a given threshold [26]. This is because the pH gradually rises as it moves from the proximal to the distal intestinal tract. The medicine is able to be released in the terminal ileum or cecum because Eudragit® S resin is a pH-sensitive polymer that disintegrates at a pH >7. On the other hand, the Eudragit® L resin dissolves at a pH lower than 6, which results in the active medication being distributed throughout the jejunum, the terminal ileum, and the colon. Within the Eudragit S capsule, the Mezavant capsules contain additional lipophilic and hydrophilic matrices that are part of the Multi Matrix System [27]. This is done with the intention of allowing for a slower diffusion of the drug through the colon. Apriso also has a polymer matrix that is coated with Eudragit L. This matrix is there so that the mesalamine can be gradually distributed throughout the colon. Pentasa is a formulation of mesalamine that features a distribution method that is not dependent on pH. This formulation is made up of microgranules of mesalamine that are encased in a semi-permeable membrane made of moisture-sensitive ethylcellulose. This membrane allows the mesalamine to be released in a pH-independent manner, starting in the duodenum and continuing all the way through the digestive system [28].

Table 1: Mesalamine Delivery Mechanisms have undergone recent advances

Sr. No.	Formulation Developed	Reported Clinical trials
1.	Mesalazine Micropellets	Pentasa
2.	Multimatrix (hydrophylic/lipophylic matrices	Salofalk
3.	Mesalamine (Tablets)	Asacol

Patients with UC can choose between long-term medicinal treatment to reduce intestine inflammation or surgical removal of the affected organ (colectomy). Some treatments can be used in either the acute phase (to induce a response and remission) or the chronic phase (to sustain remission) of illness [28-30]. Most people with UC take maintenance medication therapy to prevent relapse because there is currently no recognized 'cure' for the condition. Only patients whose condition has not responded to medical treatment or who have developed complications are candidates for a colectomy. A'step-up' method is commonly used in medical therapy, wherein patients who do not

respond to first-line medications (typically topical or oral) are given increasingly complex agents (with potentially more severe adverse effects) [31-34].

There is hope that new mesalamine formulations will increase patient adherence and the drug's effectiveness. These new 5-ASA formulations have shown efficacy in active mild to moderately active UC and in the maintenance of remission, and they can be administered less frequently or once a day and come in a variety of delivery systems, such as micropellet and MMX oral formulations, as well as rectal gel and once-daily suppository formulations [35, 36]. However, additional evidence is needed before 5-ASA formulations can be recommended for use in colonic CD, but it is anticipated that they will be widely utilized for chemoprevention of CRC in UC. Several studies have shown that these innovative formulations are safe, provide a streamlined dosing regimen, and boost patient quality of life and compliance (which translates to cost savings for the healthcare system). It is hoped that in the future, new 5-ASA preparations will be developed that modulate PPAR-gamma more efficiently. It's possible that the new formulations' efficacy in CD will be re-evaluated at higher doses [37-40].

Targeted Therapy in IBD

The colon is an excellent location for the absorption of peptides and proteins. The oral administration of peptide medications presents a number of significant challenges, the most significant of which is proteolysis [41]. However, these challenges can be mitigated by targeting the colon in drug delivery. Colon targeting had potential applications in a number of therapeutic areas, including treatment for colon cancer, ulcerative colitis, irritable bowel syndrome, and the delivery of medications that potentially have a deleterious effect on the upper gastrointestinal tract [42, 43]. The colonic distribution of the drug was initially accomplished primarily through the use of prodrugs, which were then coated with pH-sensitive and time-dependent polymers. Both Eudragit L-100 and Eudragit S-100 are utilized as an enteric coating material for the purpose of maintaining the integrity of the multi-particulates and preventing the medicine from being released in the stomach or upper intestine [44]. In patients who are experiencing acute symptoms of inflammatory bowel disease (IBD), the goal is to induce clinical remission of the condition while simultaneously enhancing quality of life. After remission has been achieved, patients get treatment that is specifically designed to keep them in remission [45-47]. In the case of UC, one of the additional goals of treatment is to reduce the patient's long-term steroid need while also lowering the patient's long-term risk of colorectal cancer. The treatment that is chosen depends on the degree and location of the disease, as well as the intestinal and extra-intestinal manifestations of the condition. If the induction therapy is not successful in controlling the syndrome within a trial period that is considered to be reasonable, then another therapeutic method ought to be tested out until the symptoms are under control and the maintenance therapy can be started [36]. The purpose of this study was to evaluate the influence of demographic factors, illness-specific characteristics, and different treatment regimens on the HRQoL of patients diagnosed with inflammatory bowel disease (IBD), namely Crohn's disease or ulcerative colitis. Healing of the mucosa is another potential target for treatment in inflammatory bowel disease (IBD), in addition to alleviating clinical symptoms. Mucosal healing is related with a modification in the natural history and illness course of both CD and UC. This results in fewer hospitalizations, reduced requirements for surgery, and decreased rates of disease complications. There is a general understanding that mucosal healing should be taken into account; however, there is no agreement over the method that is the most accurate for assessing it, and it is unknown what level of healing is necessary to affect the progression of the disease [48-50].

CONCLUSION

Remission can be induced and maintained with mesalamine in mild to moderate UC.

Additionally, it has a good safety profile and has been shown in clinical studies to improve QoL and induce mucosal healing. Although mesalamine's use as a chemoprophylaxis agent against CRC is intriguing, there is currently inconclusive evidence to support this application of the drug. In addition, inadequate adherence to mesalamine in practice is a key concern in maintenance of remission. Simplifying dose schedules for maintaining remission may increase adherence. The comparative efficacy of mesalamine is challenging to assess because of the variety of study methodologies and mesalamine formulations available. Given that UC originates in the rectum and progresses distally, the rectum should always be a therapeutic focus. Mucosal concentrations of mesalamine are increased when the drug is applied rectaly as opposed to taken orally.

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REFERENCES

1. Lautenschläger C, Schmidt C, Fischer D, Stallmach A. Drug delivery strategies in the therapy of inflammatory bowel disease. Advanced drug delivery reviews. 2014 May 1;71:58-76.
2. Basson AR, Minh L, Cominelli F. Complementary and alternative medicine (CAM) and next-generation CAM (NG-CAM) strategies for therapeutic gut microbiota modulation in inflammatory bowel disease. Gastroenterology clinics of North America. 2017 Dec;46(4):689.
3. Newton JM. Gastric emptying of multi-particulate dosage forms. International journal of pharmaceutics. 2010 Aug 16;395(1-2):2-8.
4. Di Pretoro G, Zema L, Palugan L, Wilson DI, Rough SL, Gazzaniga A. Optimization of a high strenght mesalamine multi-particulate dosage form. InAtti del 51° Simposio AFI 2011. Tipolitografia Manfredi, Varese.
5. Di Pretoro G, Zema L, Palugan L, Wilson DI, Rough SL, Gazzaniga A. Optimisation and scale-up of a highly-loaded 5-ASA multi-particulate dosage form using a factorial approach. European journal of pharmaceutical sciences. 2012 Jan 23;45(1-2):158-68.
6. Di Pretoro G, Zema L, Palugan L, Wilson DI, Rough SL, Gazzaniga A. A high strenght mesalamine multiple-unit dosage form intended for ileo-colonic delivery. THE AAPS JOURNAL. 2011:1-.
7. Andreas CJ, Chen YC, Markopoulos C, Reppas C, Dressman J. In vitro biorelevant models for evaluating modified release mesalamine products to forecast the effect of formulation and meal intake on drug release. European Journal of Pharmaceutics and Biopharmaceutics. 2015 Nov 1;97:39-50.
8. Varshosaz J, JaffarianDehkordi A, Golafshan S. Colon-specific delivery of mesalazine chitosan microspheres. Journal of microencapsulation. 2006 Jan 1;23(3):329-39.
9. Rashid F, Lichtenstein GR. New Non-anti-TNF-α Biological Therapies for the Treatment of Inflammatory Bowel Disease. Pediatric Inflammatory Bowel Disease. 2017:425-50.
10. Kumar R, Chandra A, Gautam PK. Modified approaches for colon specific drug delivery system: a review. Indian Journal of Pharmaceutical and Biological Research. 2013 Mar 31;1(03):67-79.
11. Jose S, Dhanya K, Cinu TA, Litty J, Chacko AJ. Colon targeted drug delivery: Different approaches. Journal of young pharmacists. 2009 Jan 1;1(1):13.
12. Mladenovska K. Drug and cell delivery systems in the treatment of colitis. InColitis 2012 Jan 5. IntechOpen.
13. Jangde R. Colonic drug delivery of new approaches. Research Journal of

Pharmaceutical Dosage Forms and Technology. 2011;3(6):241-6.
14. Jiang B, Yu H, Zhang Y, Feng H, Hoag SW. A Multiparticulate Delivery System for Potential Colonic Targeting Using Bovine Serum Albumin as a Model Protein: Theme: Formulation and Manufacturing of Solid Dosage Forms Guest Editors: Tony Zhou and Tonglei Li. Pharmaceutical research. 2017 Dec;34:2663-74.
15. Pithadia AB, Jain S. Treatment of inflammatory bowel disease (IBD). Pharmacological Reports. 2011 May;63(3):629-42.
16. Fakhoury M, Negrulj R, Mooranian A, Al-Salami H. Inflammatory bowel disease: clinical aspects and treatments. Journal of inflammation research. 2014 Jun 23:113-20.
17. Morgan XC, Tickle TL, Sokol H, Gevers D, Devaney KL, Ward DV, Reyes JA, Shah SA, LeLeiko N, Snapper SB, Bousvaros A. Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. Genome biology. 2012 Sep;13(9):1-8.
18. Zhang M, Viennois E, Prasad M, Zhang Y, Wang L, Zhang Z, Han MK, Xiao B, Xu C, Srinivasan S, Merlin D. Edible ginger-derived nanoparticles: A novel therapeutic approach for the prevention and treatment of inflammatory bowel disease and colitis-associated cancer. Biomaterials. 2016 Sep 1;101:321-40.
19. Ghosh S, Mitchell R. Impact of inflammatory bowel disease on quality of life: Results of the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) patient survey. Journal of Crohn's and Colitis. 2007 Sep 1;1(1):10-20.
20. Moura FA, de Andrade KQ, Dos Santos JC, Araújo OR, Goulart MO. Antioxidant therapy for treatment of inflammatory bowel disease: does it work?. Redox biology. 2015 Dec 1;6:617-39.
21. Kane SV. Systematic review: adherence issues in the treatment of ulcerative colitis. Alimentary pharmacology & therapeutics. 2006 Mar;23(5):577-85.
22. Axelrad JE, Lichtiger S, Yajnik V. Inflammatory bowel disease and cancer: The role of inflammation, immunosuppression, and cancer treatment. World journal of gastroenterology. 2016 May 5;22(20):4794.
23. Gevers D, Kugathasan S, Denson LA, Vázquez-Baeza Y, Van Treuren W, Ren B, Schwager E, Knights D, Song SJ, Yassour M, Morgan XC. The treatment-naive microbiome in new-onset Crohn's disease. Cell host & microbe. 2014 Mar 12;15(3):382-92.
24. Zhu Y, Mahon BD, Froicu M, Cantorna MT. Calcium and 1α, 25-dihydroxyvitamin D3 target the TNF-α pathway to suppress experimental inflammatory bowel disease. European journal of immunology. 2005 Jan;35(1):217-24.
25. Triantafillidis JK, Merikas E, Georgopoulos F. Current and emerging drugs for the treatment of inflammatory bowel disease. Drug design, development and therapy. 2011 Apr 6:185-210.
26. Graff LA, Walker JR, Bernstein CN. Depression and anxiety in inflammatory bowel disease: a review of comorbidity and management. Inflammatory bowel diseases. 2009 Jul 1;15(7):1105-18.
27. Schreiber S, Rutgeerts P, Fedorak RN, Khaliq–Kareemi M, Kamm MA, Boivin M, Bernstein CN, Staun M, Thomsen OØ, Innes A, Group CC. A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. Gastroenterology. 2005 Sep 1;129(3):807-18.
28. Horne R, Parham R, Driscoll R, Robinson A. Patients' attitudes to medicines and adherence to maintenance treatment in inflammatory bowel disease.

Inflammatory bowel diseases. 2009 Jun 1;15(6):837-44.
29. Sandborn WJ, Feagan BG, Stoinov S, Honiball PJ, Rutgeerts P, Mason D, Bloomfield R, Schreiber S. Certolizumab pegol for the treatment of Crohn's disease. New England journal of medicine. 2007 Jul 19;357(3):228-38.
30. Kozuch PL, Hanauer SB. Treatment of inflammatory bowel disease: a review of medical therapy. World journal of gastroenterology: WJG. 2008 Jan 1;14(3):354.
31. Clark M, Colombel JF, Feagan BC, Fedorak RN, Hanauer SB, Kamm MA, Mayer L, Regueiro C, Rutgeerts P, Sandborn WJ, Sands BE. American gastroenterological association consensus development conference on the use of biologics in the treatment of inflammatory bowel disease, June 21–23, 2006. Gastroenterology. 2007 Jul 1;133(1):312-39.
32. Friend DR. New oral delivery systems for treatment of inflammatory bowel disease. Advanced drug delivery reviews. 2005 Jan 6;57(2):247-65.
33. Sandborn WJ, Rutgeerts P, Feagan BG, Reinisch W, Olson A, Johanns J, Lu J, Horgan K, Rachmilewitz D, Hanauer SB, Lichtenstein GR. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. Gastroenterology. 2009 Oct 1;137(4):1250-60.
34. Ben-Horin S, Chowers Y. loss of response to anti-TNF treatments in Crohn's disease. Alimentary pharmacology & therapeutics. 2011 May;33(9):987-95.
35. Nguyen GC, Bernstein CN, Bitton A, Chan AK, Griffiths AM, Leontiadis GI, Geerts W, Bressler B, Butzner JD, Carrier M, Chande N. Consensus statements on the risk, prevention, and treatment of venous thromboembolism in inflammatory bowel disease: Canadian Association of Gastroenterology. Gastroenterology. 2014 Mar 1;146(3):835-48.
36. Anderson JL, Edney RJ, Whelan K. Systematic review: faecal microbiota transplantation in the management of inflammatory bowel disease. Alimentary pharmacology & therapeutics. 2012 Sep;36(6):503-16.
37. Gisbert JP, Bermejo F, Pajares R, Perez-Calle JL, Rodríguez M, Algaba A, Mancenido N, de la Morena F, Carneros JA, McNicholl AG, González-Lama Y. Oral and intravenous iron treatment in inflammatory bowel disease: hematological response and quality of life improvement. Inflammatory bowel diseases. 2009 Oct 1;15(10):1485-91.
38. Levine JS, Burakoff R. Extraintestinal manifestations of inflammatory bowel disease. Gastroenterology & hepatology. 2011 Apr;7(4):235.
39. Mladenovska K. Drug and cell delivery systems in the treatment of colitis. InColitis 2012 Jan 5. IntechOpen.
40. Chen T, Li J, Chen T, Sun CC, Zheng Y. Tablets of multi-unit pellet system for controlled drug delivery. Journal of Controlled Release. 2017 Sep 28;262:222-31.
41. Basson AR, Minh L, Cominelli F. Complementary and alternative medicine (CAM) and next-generation CAM (NG-CAM) strategies for therapeutic gut microbiota modulation in inflammatory bowel disease. Gastroenterology clinics of North America. 2017 Dec;46(4):689.
42. Ramli SH, Wong TW, Naharudin I, Bose A. Coatless alginate pellets as sustained-release drug carrier for inflammatory bowel disease treatment. Carbohydrate polymers. 2016 Nov 5;152:370-81.
43. Sahu A, Jain A, Gulbake A. Colon as Target for Drug Delivery. Current Drug Therapy. 2014 Mar 1;9(1):63-73.
44. Rashid F, Lichtenstein GR. New Non-anti-TNF-α Biological Therapies for the Treatment of Inflammatory Bowel

Disease. Pediatric Inflammatory Bowel Disease. 2017:425-50.

45. John R. *Targeted Drug Delivery of Capecitabine Microspheres for Colorectal Cancer* (Doctoral dissertation, PSG College of Pharmacy, Coimbatore).
46. Peng JC, Shen J, Ran ZH. Novel agents in the future: Therapy beyond anti-TNF agents in inflammatory bowel disease. Journal of Digestive Diseases. 2014 Nov;15(11):585-90.
47. Shah HK, Mukherji G, Bro B. Enteric coating for colonic delivery. InModified-Release Drug Delivery Technology 2008 May 28 (pp. 337-350). CRC Press.
48. Billiet T, Rutgeerts P, Ferrante M, Van Assche G, Vermeire S. Targeting TNF-α for the treatment of inflammatory bowel disease. Expert opinion on biological therapy. 2014 Jan 1;14(1):75-101.
49. Chandran S, Sanjay KS, Ali Asghar LF. Microspheres with pH modulated release: design and characterization of formulation variables for colonic delivery. Journal of microencapsulation. 2009 Aug 1;26(5):420-31.
50. Danese S, Semeraro S, Armuzzi A, Papa A, Gasbarrini A. Biological Therapies for Inflammatory Bowel Disease: Research DrivesClinics. Mini reviews in medicinal chemistry. 2006 Jul 1;6(7):771-84.