International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 13, Issue 4, 2021

Review Article

RECENT APPROACHES INVOLVED IN COLONIC DRUG TARGETING FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE: A REVIEW

SWAMINATHAN V.[1*], VAIYANA RAJESH C.[1]

[1]Department of Pharmaceutics, PSG College of Pharmacy, Coimbatore 641004, Tamilnadu, India
Email: swaminathan016@gmail.com

Received: 27 Jan 2021, Revised and Accepted: 05 May 2021

ABSTRACT

The objective of the review is to present the contemporary approaches involved in colonic drug targeting for the therapy of inflammatory bowel disease (IBD). The adverse reactions and side-effects of the conventional drug delivery systems are largely on account of the systemic absorption of the drugs from the small intestine. Moreover, in current drug delivery systems, the drug has to be frequently administered and also in larger doses which greatly reduces patient compliance. Various approaches which are being described here mainly target the colonic region specifically for improved therapy of IBD, by increasing localization and accessibility of the drug to the target site. Also, these approaches will result in the reduction of dose and minimization of adverse effects combined with the use of conventional drug delivery systems.

Keywords: Colonic drug targeting, Nucleotide delivery vehicle, Polymeric Nanocarriers, Bioadhesive pellets with pH-sensitive coating, Drug loaded nanoparticles with pH-sensitive coating

DOI: https://dx.doi.org/10.22159/ijap.2021v13i4.40893. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Inflammatory bowel disease (IBD) involves inflammatory conditions of the colon and small intestine due to inappropriate mucosal immune activation. Crohn's disease and Ulcerative colitis are the major types of IBD. Crohn's disease also called regional enteritis (because of frequent ileal involvement) affects the entire gastrointestinal tract. Ulcerative colitis affects only the colon and the rectum and extends only into the mucosa and submucosa; it occurs only in the innermost layer of the lining of the intestine [1]. The etiology of the IBD is still completely unidentified which makes its treatment a huge challenge [2]. IBD is a result of environmental and genetic factors interactions leading to immunological responses and intestinal inflammation. Dietary patterns are also a hazardous factor for ulcerative colitis [1]. Evidence suggests that the causes for uncontrolled inflammation and inadequate repair and destruction of the gut epithelium in Crohn's disease are because of the loss in commensal bacteria tolerance [2].

Symptoms of the disease depend on the type of IBD. Abdominal pain in the lower left part and diarrhea are been observed in patients with ulcerative colitis, which causes weight loss and blood on rectal examination. Pain in the lower right abdomen is observed in Crohn's disease, but with less frequent rectal bleeding than in ulcerative colitis. Despite Crohn's disease and Ulcerative colitis are different, the following symptoms are common in both: abdominal pain, diarrhea, rectal bleeding, loss of weight, and severe internal cramps/muscle spasms in the pelvic area. Anemia is the most common extraintestinal complication of inflammatory bowel disease. Stool inflammatory markers assessment followed by colonoscopy with biopsy of pathological lesions is the most common way of diagnosis.

The medical or surgical remedy is not available for IBD. Oral colon targeted drug delivery is used for the therapy of IBD, which is largely effective only in mitigating symptoms [3, 4]. Both ulcerative colitis and Crohn's disease treatment are similar, although significant differences exist including limited or lack of response and increased need for surgery in Crohn's disease [5]. Treatment mainly involves the use of medications, like immunosuppressive drugs and anti-inflammatory compounds which reduce the symptoms and decrease inflammations of the lining. But attaining remission in IBD patients remains a challenge.

Under certain conditions, when treatment using medications fails, the large intestine is removed by a surgery termed colectomy. Colectomy can cure ulcerative disease, but unfortunately, Crohn's disease can reappear after surgery. Certain side effects associated with most pharmaceutical compounds also will result in reduced patient compliance and worsening of the disease. Oral administration of anti-inflammatory drugs has been proved effective but has certain restrictions upon administering high doses, as the administered drug is delivered to nonspecific cells, which results in either infusion reactions or unsavory side effects.

Various international publications of the past few decades are summarized from the reputed sources (Elsevier, Pubmed, and NCBI) to emphasize the significance of the approaches in colonic drug targeting for the treatment of IBD. These approaches are aimed at developing drug delivery methods to distribute anti-inflammatory drugs to the areas of the most afflicted parts of the gastrointestinal tract [1]. The primary approaches for colonic drug delivery involve: (i) drugs linked covalently with polymers as a prodrug, (ii) pH-sensitive polymer (Eudragit polymers), bioadhesive polymers, or biodegradable polymeric coatings, and (iii) microbially triggered delivery of drugs. Further to the above approaches, there are novel approaches such as (i) pressure controlled delivery, (ii) CODESTM (combined approach of pH-dependent and microbially triggered delivery), (iii) osmotic drug delivery, and (iv) multiparticulate systems like microspheres and nanoparticles [6]. These approaches are developed for the therapy of IBD for increasing drug localization and accessibility of drug at the target site, reduction of dose, and side-effects associated with the conventional drug delivery systems [4, 7-10].

Table 1: Comparison of conventional drug delivery systems and novel site-specific colon targeted approaches in the treatment of IBD

Conventional drug delivery systems	Novel site-specific colon targeted approaches	Reference
Systemic absorption takes place because of delivery to non-specific cells	Systemic absorption is very low due to its site-specific nature	[1]
Side effects are possible due to systemic absorption of drugs	Very minimal side effects due to its site-specific nature	[1, 4]
High doses of the drug have to be administered for obtaining the desired therapeutic effect	Reduction of doses is possible. The desired therapeutic effect can be obtained with very low doses	[1]
Decreased patient compliance due to high frequency and dose of drugs administered	Increased patient compliance due to less frequency and dose of drugs administered	[4, 7-10]

Bioadhesive pellets of curcumin and cyclosporine with pH-sensitive coating

Bioadhesive pellets are prepared by using Curcumin, Cyclosporine, along with methacrylate copolymer (Eudragit® S100), Hydroxypropylcellulose (HPC) and Carbomer 940 (CP940) (1:1 ratio). Curcumin is used for its anti-inflammatory properties along with cyclosporine which is an immunomodulatory drug, for its synergistic effect. Bioadhesive pellets are prepared by extrusion/spheronization method with core material containing bioadhesive CP940 and HPC-H. Eudragit® S100 polymer is used to coat bioadhesive pellets, to deliver the drugs to the colon. Microcrystalline cellulose (Avicel PH101) is founded as the best core-forming agent. *In vitro* dissolution studies of coated pellets shown that 12.327±0.342 % of Curcumin and 14.751±0.112 % of Cyclosporine are released in pH 6.8 at the end of 6 h and in pH 7.4 at the end of 24 h 71.278±0.100 % of Curcumin and 76.76±0.195 % of Cyclosporine are released and follows zero-order kinetics.

The efficiency of drug-loaded pellets coated with Eudragit® S100 is evaluated on an acetic acid-induced ulcerative colitis rat model. It revealed the therapeutic efficacy of Eudragit® S100 coated bioadhesive pellets in alleviating the condition of colitis in the animal model which is reflected by weight gain along with the clinical, macroscopic, and microscopic parameters improvement of induced colitis when compared with free Curcumin and Cyclosporine [4]. Also, Curcumin and Cyclosporine combination at low doses was found to have a synergistic effect in the treatment of IBD in comparison with drugs at higher doses [11]. Hence Curcumin and Cyclosporine bioadhesive pellets with Eudragit® S100 coating may act as a tool for colon targeted delivery in the therapy and management of IBD [4].

Table 2: Various polymer and drug used in the approaches

Approach	Polymer	Drug	Reference
Bioadhesive pellets	Eudragit® S100, Hydroxypropylcellulose and Carbomer 940	Curcumin, Cyclosporine	[4]
pH-sensitive polymeric coating	Poly lactic-co-glycolic acid	Budesonide	[12]
Calcium alginate–carboxymethyl cellulose beads	Calcium alginate, Carboxymethyl cellulose beads	5-fluorouracil	[13]
Microcrystals with pH-sensitive multilayers	Chitosan, Eudragit® S100	Dexamethasone	[14]
Disulfide cross-linked nanospheres	Thiolated sodium alginate	5-amino salicylic acid	[15]
Dual pH and microbiota-triggered coating	Eudragit® S, Starch	Mesalamine	[16]
Edible ginger-derived nanoparticles	-	6-gingernol, 6-shogaol	[17]
Dual Enzyme and pH-sensitive nanoparticles	Eudragit® S, azo-polyurethane	Coumarin-6	[18]
Cyclodextrin inclusion complex	Hydroxypropyl beta-cyclodextrin	Fluticasone propionate	[20]
Microbiota sensitive coatings	Nutriose: ethylcellulose	5-amino salicylic acid	[23]
Mucus penetrating nanosuspension enema	Pluronic F127 coating	Budesonide	[24]
Tablet in capsule formulation	Hydroxypropyl methylcellulose, Eudragit E100	Mesalamine	[31, 32]
Nucleotide delivery vehicle	Cationic konjac glucomannan	Infliximab	[35]
Oral polymer Curcumin conjugate	Polyethylene glycol	Curcumin	[36]
Polymer based Oral Curcumin	Eudragit® S100	Curcumin	[37]
Superoxide dismutase/catalase mimetic nanomedicine	β-cyclodextrin	Tempol	[38]
Polymeric nanocarriers	Poly lactic-co-glycolic acid	Cyclosporine A	[39-43]

Budesonide loaded nanoparticles with pH-sensitive coating

The novel coated budesonide-loaded nanoparticles combine both the pH-sensitive and sustained drug release. Initial burst release or lack of pH sensitivity upon the oral delivery of conventional nanoparticles makes it limited for colon drug delivery. To overcome this nanoparticles with pH-sensitive polymeric coating are developed to minimize the release of the drug early in the upper part of the gastrointestinal tract. Oil in water (o/w) emulsion technique is used for the preparation of Budesonide and poly lactic-co-glycolic acid (PLGA) nanoparticles. Budesonide-loaded nanoparticles coated with pH-sensitive polymer are also prepared. Particle sizes of both the PLGA nanoparticles are found to be 200±10.1 nm and 240±14.7 nm respectively along with high encapsulation efficiency (85-90%) and a production yield of 90-94 %.

In vitro dissolution studies showed that the coated PLGA nanoparticles reduced the initial burst release at acidic pH and released the drug only at neutral and alkaline pH in comparison with the uncoated PLGA nanoparticles, which proves that coated budesonide nanoparticles will minimize the adverse effects of the drug by facilitated localized treatment via oral administration. The therapeutic efficiency of both the coated nanoparticles and plain nanoparticles is evaluated in acute and chronic colitis mouse models along with the aqueous solution of the drug. The concentration of the drug remains equal in all three formulations (0.168 mg/kg). The results obtained shows that the coated PLGA nanoparticles pacified the induced colitis better than the Plain uncoated PLGA nanoparticles, which is already more effective than the treatment with the same dose of the free drug, which proved the application of budesonide loaded nanoparticles for targeted drug delivery to the intestinal mucosa, which can be further improved for oral administration by applying pH-dependent drug release characteristics [12].

Calcium alginate–Carboxymethyl cellulose beads

Calcium alginate and carboxymethyl cellulose beads involve the mingled effects of pH sensitivity, colonic microbial degradation, and colon-specific mucoadhesivity. Both Calcium alginate and carboxymethyl cellulose are biopolymers having a pH-dependent swelling behavior. Since both are anionic, this allows them to shrink in acidic pH and to swell upon exposure to neutral or basic pH. Along with the pH sensitivity, both the polymers also possess excellent mucoadhesive properties. The beads are prepared by the ionic gelation method. 5-fluorouracil is loaded into the beads by swelling. The swelling study which is done at various pH such as 1.2, 6.8, and 7.4, have shown that the swelling is high in basic pH and low in acidic pH.

Mucoadhesive test has shown that the beads have high mucoadhesivity for colon mucosa and minimum for stomach mucosa. In vitro colonic degradation carried out using colon microflora from human stool culture, affirmed that the beads are degradable wholly in phosphate buffer pH 7.4. In vitro dissolution study of the beads showed release of drug minimum in pH 1.2 and maximum release in pH 6.8. These data when combined along with the mucoadhesivity test have shown that the complete disintegration and drug release at colonic pH are possible. 5-fluorouracil bioadhesive beads are further evaluated for their therapeutic potential using adenocarcinoma cell lines. 3-[4,5-dimethylthiazole-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay is used for the evaluation of cell viability, which showed that after 48 h cell viability reduced undoubtedly after cells are exposed to the drug-loaded beads. The data obtained suggest these bioadhesive beads can be used as a promising colon targeting tool for the therapy of IBD [13].

Dexamethasone microcrystals with pH-sensitive multilayers

Dexamethasone is used to treat mild to moderate forms of IBD. But long-term use of such corticosteroids causes serious systemic side effects.

Moreover, corticosteroid dependence and side effects are observed mainly with their systemic administration. Reduction of unwanted effects and improved local bioavailability at targeted inflamed tissues can be achieved by the use of micro and nanoparticles employing concepts of pH-sensitive polymer coating and enzyme-dependent systems. However, they suffer from poor loading efficiency due to external phase crystallization during encapsulation. To overcome this, pH-sensitive layer-by-layer (LBL) coated dexamethasone microcrystals for colon targeted delivery are prepared.

Dexamethasone microcrystals which are LBL coated using multilayers of chitosan oligosaccharide; alginate and pH-sensitive Eudragit® S100 polymer outermost coating for targeted colonic drug release and improving therapeutic efficacy. A pH-dependent drug release study is performed at different pH (1.2, 6.8, and 7.4) to closely mimic the pH of the gastrointestinal tract. For comparison the dexamethasone microcrystals without outer Eudragit® S100 coating is also prepared. The results obtained reveal that the dexamethasone microcrystals containing only chitosan/alginate multilayers show burst release in pH 1.2 and 6.8, whereas the microcrystals containing Eudragit® S100 outer coating decreases the burst release of drug in pH 1.2 and 6.8 and shows more sustained release at pH 7.4. Drug release is further studied in the presence and absence of caecal contents to confirm sufficient drug release in the colon.

As expected drug release rate of Eudragit® S100 coated dexamethasone microcrystals in contrast to the uncoated microcrystals remains unaffected in the presence of caecal contents. Dextran sulfate sodium-induced colitis model of mice is used to evaluate the *in vivo* anti-inflammatory activity of Eudragit® S100 coated dexamethasone microcrystals. It showed that the Eudragit® S100 coated microcrystals effectively mitigated the symptoms of colitis. Therefore, the Eudragit® S100 coated dexamethasone microcrystals along with chitosan/alginate multilayer, efficiently reduces the pre-colonic loss of dexamethasone and increased colon dexamethasone availability and thus makes it a potential tool for the targeted delivery to the colon especially in IBD treatment [14].

Disulfide cross-linked nanospheres

Even though many oral colon-specific drug delivery systems (OCSDDS) deliver drugs to the colon in enough concentration with no loss, the lack of selectivity to the inflamed lesions results in adverse effects. Therefore to increase the selectivity of the drug to the colonic lesions, nanospheres that are both pH-sensitive and reduction responsive are prepared for colon-specific drug delivery. Nanospheres are formulated by self-assembled amphiphilic thiolated sodium alginate (TSA) in deionized water which produces cross-linked disulfide bonds. Due to high concentrations of proteins inside the inflamed tissues with positive charges, it makes the negatively charged nanoparticles highly specific towards the inflamed tissues. Reduction cleavage of disulfide bonds in the colon causes triggered drug release from the carriers due to the standard reduction potential for the disulfide bond cleavage being lower than the reduction potential of the colon.

The nanospheres are prepared by immobilization of 4-amino thiophenol on the sodium alginate backbone which is previously oxidized to sodium periodate, which forms self-assembled nanospheres which are crossly-linked in deionized water and are investigated for pH-sensitivity, reduction-response, and cell cytotoxicity, followed by the *in vitro* dissolution study. pH-sensitivity data showed that the particle diameter of the prepared nanospheres is minimum at acidic pH and maximum at pH 7.0. Reduction response studies conducted using pH 7.4 buffer containing glutathione of various concentrations (0, 10 μmol, and 10 mmol), the nanospheres remained stable in the solution without glutathione and with 10 μmol glutathione.

In contrast, increased particle size and size distribution are noticed in a buffer solution containing millimolar glutathione. Cytotoxicity results showed no toxicity. *In vitro,* drug release studies performed using simulated gastric environment revealed that the cumulative amount of 5-amino salicylic acid released over 15 h from the microspheres is 25%, but in contrast 5-amino salicylic acid release is increased significantly, indicating the nanospheres disulfide bonds availability, which is cleaved by glutathione resulting in the increased 5-amino salicylic acid release, which can be used as a potential tool in the delivery of 5-amino salicylic acid to the inflamed colonic lesions in the therapy of IBD [15].

Dual pH and microbiota-triggered coating (Phloral™)

Dosage forms for targeted delivery of drugs to the ileocolonic region are mostly based on enteric-coating technology. However accurate targeting of inflamed colonic lesions is not possible due to individual variabilities such as fluid pH and transit times which cause enteric coating failure. To overcome this Phloral™, which combines the principles of pH-triggered release (Eudragit® S; dissolving at pH 7) and microbiota triggered (resistant starch), has been developed for the foolproof approach to colonic drug targeting. It involves the use of resistant starch in a way that the pH-triggered release and outer enteric coating condition not gets affected. Starch granules are made more digestible for bacterial enzymes by heat treating it along with butanol to disrupt the crystalline structure. Swelling of starch across the upper gut is prevented by the outer Phloral™ enteric coating.

The *in vivo* drug release studies performed using Kreb's buffer pH 7.4 by comparing with Eudragit® S coated tablets showed that the release of drug similar, indicating the absence of any effect on drug release by starch. Starch also acts as a secondary trigger, by accelerating the release of drugs by its degradation due to colonic bacteria; even though the pH of the colon in ulcerative colitis patients is low. This dual pH-enzymatic trigger coating provides an alternative way for colon-specific drug delivery despite the challenging conditions, such as reserved exposure to high pH in the distal intestine fluid and rapid transport across the colon, which will provide an exceptional delivery approach in treating IBD and other associated diseases [16].

Edible ginger-derived nanoparticles

Existing treatment options for IBD include the use of anti-inflammatory medications or immune suppressants. Despite these medications are effective their use remains narrow due to their indifferent immunological effects cause side effects such as nausea, allergic reactions, pancreatitis, and other life-threatening side effects. Also locally acting anti-inflammatory drugs with systemic absorption require high doses. Moreover sustained release dosage forms for colon-specific drug delivery are only effective in a particular subset of IBD patients. Anti-TNF-α agents are highly effective but their application is limited needed because they have to be systemically administered.

Naturally, derived nanoparticles are both safe and profitable when compared with the restrictions of artificially derived nanoparticles such as toxic effects and limited manufacturing scale. 6-gingernol and 6-shogaol obtained from the ginger possess anti-oxidative, anti-inflammatory, and anti-cancer activity. For treatment of IBD, the therapeutic efficiency of ginger-derived nanoparticles is examined. The prepared ginger nanoparticles are found stable in simulated gastric and intestinal conditions. Oral administration of the nanoparticles showed that they are retained in the colon which is of potential use in the treatment of IBD. Also, the ginger nanoparticles prevented the signs of inflammation at the histological level in drug-induced colitis mice model.

For analyzing potential toxicity colon-26 epithelial cell lines are used and as expected orally administered nanoparticles showed no effects in both intestinal epithelial cell proliferation and apoptosis. Orally administered ginger-derived nanoparticles target the colon efficiently and are taken up by epithelial cells and promoted mucosal healing in the colitis induced mice model. Also, it reduces colorectal tumors by inhibiting levels of cytokine, intestinal epithelial cell proliferation, and apoptosis. Thus ginger derived nanoparticles can be developed on large scale and represent an effective therapeutic strategy for therapy and management of IBD [17].

Dual enzyme and pH-sensitive nanoparticles

In the treatment of IBD specific colonic drug delivery is desired for increasing the drug availability. Increased elimination due to IBD

associated high frequency diarrhea diminishes the ability of current dosage forms to deliver drugs to the inflamed colon. The majority of the commercialized colon drug delivery systems depend on pH changes in the digestive tract to deliver the drugs by using methacrylate copolymer (Eudragit® S 100). But sometimes the premature release of the drug from the above system causes systemic absorption of the drug, resulting in side effects. So to overcome these disadvantages, dual-sensitive nanoparticles were prepared by applying both pH-sensitive Eudragit® S and enzyme degradable azo-polyurethane using Coumarin-6 as a model drug [18].

Nanoparticles can accumulate in inflamed colon tissues and the combination helps in preventing immediate release in the stomach and facilitates the release only to the inflamed tissues by degradation of Eudragit® S-Azo-polyurethane nanoparticles prepared by O/W emulsion/solvent evaporation [18, 19]. The nanoparticles are then evaluated in buffers of various pH values (pH 1.2, 4.0, and 7.4) for detecting pH-dependent morphological changes. At pH 1.2 and 4.0, the nanoparticles showed no signs of any morphological changes. Nanoparticles quickly dissolved, exhibited swelling, and maintained their morphology in pH 7.4 which implies their ability to reach the colon in particulate form. pH-dependent drug release study done in comparison with the plain Eudragit® S coated (without azo-polyurethane) nanoparticles showed that at pH 1.2 and 4.0 the release of drug from the nanoparticles is less.

At pH 7.4 the Eudragit® S coated nanoparticles with azo-polyurethane, in contrast to the Eudragit® S coated showed no burst release and drug released more consistently. It shows that Eudragit® S coated nanoparticles with azo-polyurethane can retain the entrapped drug from the stomach and can release the drug in the colon efficiently which increases the drug availability desirable for the targeted colon delivery. The release study performed using rat gastrointestinal tract showed the ability of formulated nanoparticles achieves significantly high drug levels in the inflamed colon. These data suggest that Dual enzyme/pH-sensitive polymeric nanoparticles provide a suitable tool for colon-specific drug delivery for IBD [18].

Cyclodextrin inclusion complex

Even though glucocorticoids form an important part of the therapy of IBD, they produce systemic side effects such as dyspepsia, moon-face, hypertension, acne, insomnia, mood disturbances, and impaired glucose tolerance. Retention enemas and foam preparations are developed to avert these side effects. Fluticasone propionate is used topically for IBD, but it undergoes extensive first-pass metabolism when given by oral route. Its low aqueous solubility does not permit mucosal transport of the drug, which leads to its poor oral absorption, which can be improved using a local drug transport to the inflamed tissues.

Molecules of a certain size and shape along with the cyclodextrin form inclusion complexes. Because of water molecules release from cyclodextrin by the drug molecules and by attaining apolar-apolar association it improves the aqueous solubility of the poorly aqueous soluble drug. Hydroxypropyl beta-cyclodextrin, a derivative of cyclodextrin with improved aqueous solubility and decreased nephrotoxicity is selected is coated with Eudragit S 100. The intrinsic dissolution studies showed a practically 18 times rise in the dissolution of the drug upon complexation with Hydroxypropyl beta-cyclodextrin, which is due to the complexation of the drug converts crystalline into an amorphous form. *In vitro* dissolution studies showed zero release in 0.01 N HCl, which indicates the resistance of coated granules. In phosphate buffer pH 7.4, after 15 min the release of the drug takes place with a burst release.

Drug transport studies performed *in vitro* using rat colon show drug movement in inclusion complex across the membranes which are due to the increased drug solubility at the mucosal surface, upon formulation as an inclusion complex. These outcomes show that the above proposed inclusion complex can act as a colon targeted delivery system for the therapy of IBD [20].

Microbiota sensitive coatings

Various advanced types of systems are proposed for colon-specific delivery, mainly pH-sensitive membranes, film coatings having time-dependent permeability, pressure-sensitive film coatings, and preferentially bacterial enzymes degraded film coatings. Novel polymeric coatings are also developed to adapt to the pathophysiology of IBD patients. These film coating systems are enzymatically degraded in the affected colon. The 5-Amino salicylic acid (5-ASA) pellets with Nutriose: ethylcellulose coating [21, 22] has *in vitro* ability of retarding the release of drug in the gastric and small intestinal environment, and the release only happens upon exposure to media containing fresh fecal samples of patients. Macroscopic and histological evaluation is done by using rat colitis model and inflammatory markers measurement by Enzyme-linked immunosorbent assay (ELISA) and real-time polymerase chain reaction test (PCR) to determine *in vivo* efficacy of these coated pellets to treat inflammation.

The active metabolite N-acetyl 5-ASA plasma concentration measured acts as an indicator to find the amount of drug released in the upper part of the gastrointestinal tract which is undesired. The severity of inflammation is significantly lowered by Nutriose: ethylcellulose pellets, much better in comparison with non-treated colitis group and Pentasa treated group as revealed by the macroscopic and histological evaluations which indicate the effectiveness of the developed colon targeting system. It also prevents drug release in the upper gastrointestinal tract and allows efficient targeting of the colon. The tissue sections showed that all the layers of the "vehicle-treated group" remained intact and in the "non-treated colitis group" exhibited severe signs of inflammation and also it remained the same in Pentasa treated groups.

The measurement of pro-inflammatory markers in colon tissues showed that when treated with Nutriose: ethylcellulose pellets it is significantly low when compared with those treated with Pentasa or placebo pellets, by which *in vivo* efficacy of the proposed colon targeting system is also proved. Also increased 3-Hydroxy-3-Methylglutaryl-CoA Synthase (HMG CS2) messenger ribonucleic acid (mRNA) and PPAR-γ (Peroxisome Proliferator-Activated Receptor-γ) value indicates maximized gene and receptor activation and also increase in the concentration of 5-ASA at the targeted site. N-acetyl 5-ASA plasma concentration is much lower upon treatment with the Nutriose: ethylcellulose pellets when compared with the rats receiving Pentasa pellets indicating that the proposed system effectively suppresses the release of 5-ASA in the upper part of the gastrointestinal tract since 5-ASA is actively converted into N-acetyl 5-ASA in the stomach. All these data prove the efficiency of Nutriose: ethylcellulose microbiota-sensitive film coatings for colon targeting in the treatment of IBD [23].

Mucus penetrating nanosuspension enema

For the treatment of active distal IBD locally administered micronized budesonide enema is one of the most common approaches. However, the micronized particles are limited for drug delivery to the inflamed tissues before clearance because they are large for penetrating the mucosal layer effectively. So for penetrating the mucus layer effectively and for increased drug delivery to the colon, it is formulated as nanosuspension with much inert Pluronic F127 coating for providing increased mucosal distribution and tissue penetration. The wet-milling method is used for preparing the budesonide nanosuspension coated with muco-inert Pluronic F127 as well as a budesonide micro-suspension stabilized with Polyvinylpyrollidone which is used in the clinical application.

The *in vivo* efficacy of the nanosuspension prepared is evaluated in trinitrobenzene sulfonic acid (TNBS) induced IBD. Treatment with budesonide nanosuspension results in a major reduction of macroscopic and microscopic symptoms of IBD compared to mice treated with the micro-suspension enema. Also, budesonide nanosuspension enema efficiently decreased the levels of inflammatory macrophages and Interleukin-β producing conventional dendritic 11b+cells in inflamed colon tissue in comparison to the micro-suspension enema treated mice. This indicates that the nanosuspension size and the muco-inert coating allowed increased delivery of the budesonide to the inflamed colon tissues and can be used as an alternative approach for targeting the colon in the therapy of IBD [24].

Tablet in capsule formulation

Mesalamine, the most commonly used drug for the treatment of IBD has to be administered frequently due to its large dose, which causes poor patient compliance. The Mesalamine enteric-coated pH-dependent system is used for clinical application in the IBD treatment. However due to both the increased intestinal pH variability and acidic nature of the colon in IBD patients remains a challenge in achieving colonic drug targeting, by causing variability *in vivo* performance, site of disintegration, and also the appearance of commercially available enteric-coated tablets in the stools [25-29].

Hence for reducing both the dose and administration frequency and for efficiently delivering drugs to the site of action, the tablet-in-capsule system is developed consisting of enteric-coated hydroxypropyl methylcellulose (HPMC) capsules containing four units of core tablets each with 150 mg of Mesalamine, so that each capsule delivers 600 mg of Mesalamine which greatly reduces the frequency of administration and improves patient compliance. HPMC controls the Mesalamine release from the tablets [30], which is then further coated with Eudragit E100 polymer. Overall the release time from the capsules after it reaches the colon is found to be 7 h, 8 h, 9 h, and 10 h from 1st, 2nd, 3^{rd,} and 4th unit respectively which is in par with the colon passage time of tablets (15-16 h) [31].

The *in vitro* drug release study showed that the enteric coating remained stable in the acidic pH and the release of the drug occurred only above pH 6.4. The *in vivo* study to evaluate the efficiency of the formulated capsules to release the Mesalamine is done by using the rabbit as an animal model. The roentgenographic study revealed that the capsules coated with Eudragit E 100 remain unscathed as far as the distal small intestine and the release from the capsule occurs only in the colon, which indicates that it can specifically deliver the drugs to the colon and will provide an alternative approach in colonic drug targeting in the treatment of IBD [32].

Nucleotide delivery vehicle

Tumor necrosis factor-α (TNF-α), a cytokine also has an important role in the pathogenesis of inflammation of Colon in IBD patients. In IBD patients increased levels of TNF-α causes the production of other pro-inflammatory cytokines. TNF-α blocking strategies have shown great potential for the treatment of IBD. A notable example is Infliximab which exhibits gratifying results in treating IBD in clinical trials [33]. But upon systemic administration, it causes immunodeficiency-related infections and generation of anti-drug-antibodies. So they are needed to be limited at the specific site of inflammation even though they are effective.

Hence orally-administered system for targeted delivery of anti-TNF-α nucleotides to colonic macrophages has been developed. It consists of–i) cationic konjac glucomannan (cKGM), a soluble fiber extracted from *Amorphophallus konjac,* ii) phytagel, and iii) an antisense molecule (ASO) against TNF-α. cKGM has many functions, it forms nano-complex core by conjugation with negatively charged ASO, second, it has mannose moieties which are recognized by mannose receptors in the macrophages, resulting interaction causes the phagocytosis, also cKGM shows increased water absorption and immediately swells [34]. Phytagel in contrast swells poorly and this contrast swelling property results in collapse of the system in the colon.

The prepared formulation showed less toxicity when checked for cytotoxicity. *In vitro* transfection study done to observe the transfection efficiency of cKGM and ASO in macrophages and colonic epithelial cells, showed that cKGM greatly increased the transfection of ASO, which shows that cKGM may produce antisense molecule transport partly through mannose mediated endocytosis. Tissue distribution and cellular localization studies done in mice showed the enhanced aggregation of antisense molecules in the colon. Immunofluorescence staining study showed that TNF-α level in the mucosa are greatly reduced. Marked histological development is apparent when treated with antisense molecule containing cKGM in colitis-induced mice. These results suggest the potential of this cKGM containing system as an advantageous route allowing the highly effective colonic nucleic acid drug delivery which will be useful in the colonic drug targeting for the treatment of IBD [35].

Oral polymer curcumin conjugate

Various natural products have been investigated for their application in treating IBD, to overcome the soaring price, adverse effects, and nonspecific effects of the synthetic drugs after administration. Curcumin obtained from rhizomes of *Curcuma longa*, is currently having high consideration for treating IBD due to its lowering cost, steady sources, and also for its excellent anti-inflammatory activity, which is reported in many clinical trials. But its clinical application for the treatment of IBD remains a challenge due to its meagre aqueous solubility and bioavailability.

So an effective delivery system involving nanoparticles has been developed for improved colonic tissue targeting, better therapeutic efficacy, and reduced unwanted effects. Nano-sized delivery systems are employed because of their advantageous aggregation in the inflamed colonic tissues (especially size of ~100 nm). It is prepared by condensation polymerization reaction which involves the formation of disulfide bonds between hydrophobic Curcumin and hydrophilic polyethylene glycol. The release of Curcumin is by the reduction of the drug-polymer conjugate by the colonic bacteria. This nano size and neutral charged surface results in precise colonic tissue deposition, along with enhanced partition coefficient which facilitates transmembrane transport and increased oral availability.

The polymer Curcumin conjugate is then evaluated both *in vivo* and *in vitro. In vitro* release studies showed release of drug less in gastric fluid and high release in medium with rat caecal contents. *In vivo* studies for evaluating therapeutic efficiency using murine IBD, model showed that the polymer-drug conjugate significantly alleviates the induced colitis in mice which is illustrated by multifaceted regulation and mediation of IBD-related indicators. Results from both the *in vivo* and *in vitro* studies showed that polymer-drug conjugate possesses suitable physicochemical properties to overcome the gastric environment for providing preferential accumulation in the inflamed intestinal tissues, which gives us an alternative approach for the treatment of IBD [36].

Polymer based oral curcumin (Ora-Curcumin-S)

Current treatment for IBD focuses only on the established disease but cannot thwart or restrict its advancement. To specifically target the luminal side of the colon for restricting and/or managing IBD, polymer based Ora-Curcumin-S is investigated. It is developed by molecular expression of Curcumin and Eudragit® S100 by co-precipitation method in which Curcumin becomes non-crystalline because of non-covalent polymeric interactions. It is different from solid dispersions, because in polymer-drug complex despite dissolving in aqueous buffers the interactions are maintained. Ora-Curcumin-S has 1000 times enhanced aqueous solubility relative to Curcumin and soluble only above pH 6.8 (pH-dependent). 90% of Ora-Curcumin-S remained stable in phosphate buffer pH 7.4 as well as in intestinal fluid after 24 h as opposed to 10-20% unformulated Curcumin.

The formulated Ora-Curcumin-S is a Toll-like receptor-4 (TLR-4) antagonist as it inhibits Monophosphoryl lipid-A and E-coli influenced inflammatory effects in dendritic cells and cells over expressing TLR-4. Preliminary pharmacokinetic studies confirmed colon targeted delivery of soluble Curcumin to the colon with no systemic circulation exposure. Also, Ora-Curcumin-S remarkably prevents colitis and linked injury in a mouse model which is assessed by diverse preclinical parameters such as colonoscopy pictures, body weight, spleen weight, colon length and edema, pro-inflammatory signaling, and independent pathological scoring. This study showed that Ora-Curcumin-S provides a locally targeted pathway for IBD treatment, which reduces both inflammation and vulnerability to colitis associated colorectal cancer [37].

Superoxide dismutase/catalase mimetic nanomedicine

Oxidative stress which is due to the over a generation of reactive oxygen species (ROS) causes IBD initiation and progression. A superoxide dismutase/catalase mimetic nanomedicine with hydrogen peroxide-eliminating nanomatrix and free radical scavenger Tempol is developed. Oxidation-responsive β-cyclodextrin material is added to the above to form Tempol loaded

oxidation-responsive β-cyclodextrin nanoparticle (Tpl/OxbCD). On-demand release of Tempol from molecules of Tpl/OxbCD is triggered by hydrolysis of oxidation-responsive β-cyclodextrin material. The Tpl/OxbCD efficiently accumulates in the inflamed mice colon, whereby it reduces nonspecific distribution after oral delivery. Oral administration of the Tpl/OxbCD lessened colitis-related manifestations and abolished proinflammatory mediators in colitis induced mice models upon oral administration with superior efficacy over free tempol. The Tpl/OxbCD can be applied as an effective nanomedicine for the treatment of IBD and other related conditions [38].

Polymeric nanocarriers

For ideal treatment in IBD, a maximum concentration of drug in the affected tissue is needed, which is difficult when the target tissue acts as an absorptive tissue, where the drug is instantly absorbed from the intestinal lumen into the systemic circulation. Corticosteroids used for inducing remission and to prevent relapses cannot be given over large periods of time because of their systemic side effects [39]. This can be overcome by specific targeting of drugs to the affected tissues by formulating into nanoparticles.

Cyclosporine A an immunosuppressive drug causes serious side effects [40-42] that are minimized by formulating into nanoparticles, which are being processed by nanoprecipitation method, and for microparticles, nanospray drying is used. PLGA is the polymer involved which is biodegradable and applied in various pharmaceutical products. The therapeutic efficacy study is carried out using a dextran sodium sulfate (DSS) induced colitis model in comparison with a marketed oral formulation and also with drug-free Nanoparticle and Microparticles. The histopathological analysis demonstrated that the cyclosporine nanoparticles provided better remedial and shielding effect on mice mucosa than microparticles and commercially available formulation, which can be seen by mitigated manifestations related to colitis, and suppressed pro-inflammatory mediators in colitis induced mice models.

There is a significant improvement in the shielding effect of cyclosporine A on the intestinal animal mucosa when compared with other formulations. Plasma level quantifications showed that the drug is localized in the target area and not absorbed systemically. These results combinedly reveal the true potential of polymeric nanoparticles as a productive proposition for colonic drug targeting in IBD therapy and other associated conditions [43].

Nanostructured lipid carriers

Vitamin D_3 (calcitriol) or 1,25-dihydroxycholecalciferol is found deficient in serum of IBD patients, mainly with Crohn's disease, which is doubted to play an important role in IBD pathogenesis and development. *In vitro* investigations using IBD animal models disclosed that vitamin D_3 suppressed IBD development by 1) innate and acquired immunity suppression by direct and regulation of cytokine-mediated immune cells 2) mucosal barrier healing by impacting intestinal epithelium 3) maintaining gut microbiome balance by initiating antimicrobial peptides secretion from macrophages and paneth cells, which makes it beneficial in comparison to the current drugs. However clinical trials revealed that large doses of vitamin D_3 or its prodrug are required to improve the symptoms of Crohn's disease and to reduce relapse rate. But a high dose of vitamin D_3 produces hypercalcemia and other associated side effects [44].

Hence efficient transit is developed by using nanostructured lipid carriers so that the dose administered gets reduced. The principle behind these carriers is that they remain strong in gastric fluid, but steadily gets degenerated by intestinal enzyme lipase that is present in the intestinal fluids, which simultaneously intensifies the vitamin D_3 intestinal absorption. Since vitamin D_3 is not stable at high temperatures and the use of ultra-sonication is not desired due to the generation of radical species, nanostructured lipid carriers are prepared by the O/W emulsion method. *In vitro* studies revealed that the nanostructured lipid carriers containing vitamin D_3 are actively up taken by the macrophages in the inflamed lesions but showed no toxicity. Also, the nanostructured lipid carriers showed an anti-inflammatory effect by activating the nuclear factor kappa light chain enhancer of the activated B cells (NF-kβ) pathway. Upon comparison with saline dispersion, the nanostructured lipid carriers significantly increased the colonic concentrations of vitamin D_3 and also maintained the level for 12 h which shows the sustained release of vitamin D_3 by the nanostructured lipid carriers. The nanostructured lipid carriers also undoubtedly repressed the disease development in the DSS-induced colitis model. These results show that the nanostructured lipid carriers offer an alternative pathway for the treatment of IBD by acting through a different mechanism from the currently available drugs and its potential in the therapy of IBD [45].

CONCLUSION

The above discussed approaches differ from the conventional approach used for the treatment of IBD, either by offering a new drug delivery system for already available drugs or by the use of a natural substitute for efficient colonic drug targeting. The suitability of the above mentioned systems for clinical treatment remains a huge doubt. Even though the above mentioned studies revealed the potential of these approaches as a substitute for the IBD treatment, it is undeniable that the targeting effectiveness of these approaches concerned still requires to be improved. Further developmental studies are needed to be carried out for the clinical application of these approaches in IBD therapy.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors contributed equally.

CONFLICTS OF INTERESTS

Declared none

REFERENCES

1. Marc Fakhoury, Rebecca Negurlij, Armin Mooranian, Hani Al-salami. Inflammatory bowel disease: clinical aspects and treatments. J Inflamm Res 2014;7:113-20.
2. Rutgeerts P, Geboes K. Understanding inflammatory bowel disease-the clinician's perspective. Eur J Surg Suppl 2001;586:66-72.
3. Vilela EG, Torres HO, Martins FP, Ferrari Mde L, Andrade MM, Cunha AS. Evaluation of inflammatory activity in Crohn's disease and ulcerative colitis. World J Gastroenterol 2012;18:872-81.
4. Desai N, Momin M. Colon targeted bioadhesive pellets of curcumin and cyclosporine for improved management of inflammatory bowel disease. Drug Delivery Transl Res 2020;10:1288-301.
5. Burger D, Travis S. Conventional medical management of inflammatory bowel disease. Gastroenterology 2011;140:1827-37.
6. K Philip, B Philip. Colon targeted drug delivery systems: a review on primary and novel approaches. Oman Med J 2010;25:79-87.
7. Sohail M, Mudassir, Minhas MU, Khan S, Hussain Z, de Matas M, *et al.* Natural and synthetic polymer-based smart biomaterials for management of ulcerative colitis: a review of recent developments and future prospects. Drug Delivery Transl Res 2019;9:595-614.
8. Rangari TK, Puranik PK. Development of multiparticulate formulation and evaluation of colon targeted drug delivery system of ciprofloxacin: *in vivo* study with induced colitis model in rats. Asian J Pharm Clin Res 2017;10:167-85.
9. Rangari TK, Puranik PK. Development of multiparticulate formulation and evaluation of colon targeted drug delivery system of Ketoprofen: *in vivo* study with induced colitis model in rats and gamma scintigraphy. Asian J Pharm Clin Res 2016;9:234-52.
10. Laham SAA. The curative effect of methylsulfonylmethane on an experimental model of ulcerative colitis in rats. Int J Curr Pharm Sci 2019;11:51-4.
11. Ali T, Shakir F, Morton J. Curcumin and inflammatory bowel disease: biological mechanisms and clinical implication. Digestion 2012;85:249–55.

12. Ali H, Weigmann B, Neurath MF, Collnot EM, Windbergs M, Lehr CM. Budesonide loaded nanoparticles with pH-sensitive coating for improved mucosal targeting in mouse models of inflammatory bowel diseases. J Controlled Release 2014;183:167-77.
13. Agarwal T, Narayana SNGH, Pal K, Pramanik K, Giri S, Banerjee I. Calcium alginate-carboxymethyl cellulose beads for colon targeted drug delivery. Int J Biol Macromol 2015;75:409-17.
14. Oshi MA, Naeem M, Bae J, Kim J, Lee J, Hasan N, *et al.* Colon-targeted dexamethasone microcrystals with pH-sensitive chitosan/alginate/Eudragit S multilayers for the treatment of inflammatory bowel disease. Carbohydr Polym 2018;198:434-42.
15. Dan Chang, Jing Lei, Huiran Cui, Na Lu, Yanjuan Sun, Xiaohua Zhang, *et al.* Disulfide cross-linked nanospheres from sodium alginate derivative for inflammatory bowel disease: preparation, characterization and *in vitro* drug release behavior. Carbohydr Polym 2012;88:663-9.
16. Varum F, Freire AC, Fadda HM, Bravo R, Basit AW. A dual pH and microbiota-triggered coating (Phloral™) for fail safe colonic drug release. Int J Pharm 2020;583:1-8.
17. Mingzhen Zhang, Emilie Viennois, Meena Prasad, Yunchen Zhang, Lixin Wang, Zhan Zhang, *et al.* Edible ginger-derived nanoparticles: a novel therapeutic approach for the prevention and treatment of inflammatory bowel disease and colitis-associated cancer. Biomaterials 2016;101:321-40.
18. Naeem M, Kim W, Cao J, Yoo JW. Enzyme/pH dual sensitive polymeric nanoparticles for targeted drug delivery to the inflamed colon. Collods Surf B 2014:123:271-8.
19. McConnell EL, Fadda HM, Basit AW. Gut instincts: explorations in intestinal physiology and drug delivery. Int J Pharm 2008;364:213-26.
20. Thakral NK, Ray AR, Jacobsen J, Bar-Shalom D, Eriksson AH, Majumdar DK. Colon targeting of fluticasone propionate inclusion complex: a novel approach in inflammatory bowel disease. J Incl Phenom Macrocycl Chem 2013;75:175-84.
21. Karrout Y, Neut C, Wils D, Siepmann F, Deremaux L. Novel polymeric film coatings for colon targeting: drug release from coated pellets. Eur J Pharm Biopharm 2009;37:427-33.
22. Karrout Y, Neut C, Wils D, Siepmann F. Peas starch-based film coatings for site-specific drug delivery to the colon. J Appl Polym Sci 2011;119:1176-84.
23. Karrout Y, Dubuquoy L, Piveteau C, Siepmann F. *In vivo* efficacy of microbiota-sensitive coatings for colon targeting: a promising tool for IBD therapy. J Controlled Release 2015;197:121-30.
24. Date AA, Halpert G, Babu T, Ortiz J, Kanvinde P, Dimitrion P, *et al.* Mucus-penetrating nanosuspension enema for local treatment of inflammatory bowel disease. Biomaterials 2018;185:97-105.
25. Wilding IR. A scintigraphic study to evaluate what happens to pentasa and asacol in the human gut. Pract Gastroenterol 1999;23:1-8.
26. Sciarretta G, Furno A, Mazzoni M, Ferrieri A. Scintigraphic study of gastrointestinal transit and disintegration sites of mesalazine tablets labeled with technetium-99m. Scand J Gastroenterol 1993;28:783-5.
27. Basit AW. Advances in colonic drug delivery. Drugs 2005;65:1991-2007.
28. Sinha A, Ball D, Connor AL, Nightingale J, Wilding IR. Intestinal performance of two mesalamine formulations in patients with active ulcerative colitis as assessed by gamma scintigraphy. Pract Gastroenterol 2003;27:56-69.
29. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987;317:1625-9.
30. Davis SS, Robertson C, Wilding IR. Gastrointestinal transit of a multiparticulate tablet formulation in patients with active ulcerative colitis. Int J Pharm 1991;68:199-204.
31. Abrahamsson B, Alpsten M, Jonsson UE, Lundberg PJ. Gastrointestinal transit of a multiple unit formulation (metoprolol CR/ZOK) and a non-disintegrating tablet with emphasis on colon. Int J Pharm 1996;140:229-35.
32. Patel MM, Amin AF. Development of a novel tablet-in-capsule formulation of mesalamine for inflammatory bowel disease. Pharm Dev Technol 2013;18:390-400.
33. Travassos WJ, Cheifetz AS. Infliximab: use in inflammatory bowel disease. Curr Treat Options Gastroenterol 2005;8:187-96.
34. Keithley J, Swanson B. Glucomannan and obesity: a critical review. Altern Ther Health Med 2005;11:30-4.
35. Huang Z, Gan J, Jia L, Guo G, Wang C, Zang Y, *et al.* An orally administered nucleotide-delivery vehicle targeting colonic macrophages for the treatment of inflammatory bowel disease. Biomaterials 2015;48:26-36.
36. Qiao H, Fang D, Chen J, Sun Y, Kang C, Di L, *et al.* Orally delivered polycurcumin responsive to bacterial reduction for targeted therapy of inflammatory bowel disease. Drug Delivery 2016;24:233-42.
37. Kesharwani SS, Ahmad R, Bakkari MA, Rajput MKS, Dachineni R, Valiveti CK, *et al.* Site-directed polymer-drug complexes for inflammatory bowel diseases (IBD): Formulation development, characterization, and pharmacological evaluation. J Controlled Release 2018;290:165-79.
38. Zhang Q, Tao H, Lin Y, Hu Y, An H, Zhang D, *et al.* A superoxide dismutase/catalase mimetic nanomedicine for targeted therapy of inflammatory bowel disease. Biomaterials 2016;105:206-21.
39. Grimpen F, Pavli P. Advances in the management of inflammatory bowel disease. Intern Med J 2010;40:258-64.
40. Herrlinger K, Wittig B, Stange EF. Chronic inflammatory intestinal diseases. Pathophysiol Ther Int 2009;50:1229-46.
41. Kornbluth A. Cyclosporine in inflammatory bowel disease. Curr Gastroenterol Rep 1999;1:486-90.
42. Clark M, Colombel JF, Feagan BC, Fedorak RN, Hanauer SB, Kamm MA, *et al.* American gastroenterological association consensus development conference on the use of biologics in the treatment of inflammatory bowel disease. Gastroenterology 2007;133:312-39.
43. Melero A, Draheim C, Hansen S, Giner E, Carrerras JJ, Talens Visconti R, *et al.* Targeted delivery of cyclosporine a by polymeric nanocarriers improves the therapy of inflammatory bowel disease in a relevant mouse model. Eur J Pharm Biopharm 2017;119:361-71.
44. Raftery T, O'Sullivan M. Optimum vitamin D levels in Crohn's disease: a review. Proc Nutr Soc 2015;74:56-66.
45. Zai K, Hirota M, Yamada T, Ishihara N, Mori T, Kishimura A, *et al.* Therapeutic effect of vitamin D_3-containing nanostructured lipid carriers on inflammatory bowel disease. J Controlled Release 2018;286:94-102.