Advances in the treatment of inflammatory bowel disease: Focus on polysaccharide nanoparticulate drug delivery systems

Hicheme Hadji, Kawthar Bouchemal

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Hicheme Hadji, Kawthar Bouchemal *

Institut Galien Paris Saclay, CNRS UMR 8612, Université Paris-Saclay, Faculté de Pharmacie, 5 rue J-B Clément, 92296, Châtenay-Malabry France

Corresponding Author

* kawthar.bouchemal@universite-paris-saclay.fr

Abstract

The complex pathogenesis of inflammatory bowel disease (IBD) explains the several hurdles for finding an efficient approach to cure it. Nowadays, therapeutic protocols aim to reduce inflammation during the hot phase or maintain remission during the cold phase. Nonetheless, these drugs suffer from severe side effects or poor efficacy due to low bioavailability in the inflamed region of the intestinal tract. New protocols based on antibodies that target proinflammatory cytokines are clinically relevant. However, besides being expensive, their use is associated with a primary nonresponse or a loss of response following a long administration period. Accordingly, many researchers exploited the physiological changes of the mucosal barrier for designing nanoparticulate drug delivery systems to target inflamed tissues. Others exploited biocompatibility and relative affordability of polysaccharides to test their intrinsic anti-inflammatory and healing properties in IBD models. This critical review updates state of the art on advances in IBD treatment. Data on using polysaccharide nanoparticulate drug delivery systems for IBD treatment are reviewed and discussed.

Keywords: Inflammatory bowel disease; Nanoparticles; Drug delivery systems; Polysaccharides.

Contents

Introduction

Inflammatory bowel disease (IBD) is a broad term used to describe a chronic inflammatory state that occurs mainly in the colon, although the other portions of the intestinal tract were also concerned. IBD mainly encompasses two inflammatory conditions, either ulcerative colitis (UC) or Crohn's disease (CD). From an anatomical point of view, UC patients mainly suffer from an inflammation of the rectal and sigmoid colon.[1, 2] In contrast, the ileo-caecal area remains the most affected region in CD,[3, 4] although many cases have also been reported in the small intestine.[5] Another aspect that characterizes CD is the skip lesions, where the affected region alternates between inflamed and non-inflamed segments.[6] From a histological point of view, UC is a superficial inflammation, whereases CD is transmural, affecting all the layers of the colon, which makes the complications more severe.[7, 8]

Despite the tremendous efforts made to comprehend the pathophysiological state triggering the occurrence of IBD, the exact etiology remains unclear. Up to date, several parameters are incriminated as potential causative factors. They can be classified as being either endogenous or exogenous. Endogenous factors are mainly represented by genetic predisposition or immunoregulatory disorders. However, several studies suggested that microbiome dysregulation could also have a considerable impact on the development of IBD.[9, 10] Exogenous factors, on the other hand, are linked to exposure to external stress.[11] The stress can be environmental (e.g., alcohol, chemicals, drugs, industrial diet style), psychological (e.g., depression, anxiety), or even microbial through the intestine invasion by pathogenic bacteria.

With more than 6.8 million people suffering from the complications of IBD at a global scale,[12] a curative treatment of this pathology is still missing, and current treatment protocol aims at relieving acute attacks (e.g., the combination of 5-aminosalicylic acid (5-ASA) and corticosteroids, TNF-α antibodies) or preventing relapse episodes (e.g., 5-ASA therapy for UC and corticosteroids for CD). However, the active pharmaceutical ingredients (API) delivery still rests on conventional drug delivery systems (DDS) such as tablets, capsules, enemas, or solutions. These formulations have shown several limitations as the yield of the API in the colonic region is low.[13, 14] Consequently, working on alternative therapeutic approaches remains necessary to offer a better treatment protocol and reduce patient discomfort while diminishing the multiple administrations of medications or the recurrence to less hospitalization.

Over the last decade, many researchers have taken advantage of the rapid technological advances in nanomedicine by designing novel DDS. The DDS aim at enhancing the drug concentration in the targeted region through the control of API release or cell-specific targeting strategies.[15] However, many of these new approaches have failed to circumvent the several hurdles of the gastro-intestinal (GI) tract microenvironment in IBD-suffering patients. In this context, nanoparticles composed of polysaccharides showed promising results to alleviate IBD. They combine the advantages of nanoparticulate systems with intrinsic biological activities of polysaccharides. On one side, the nanoparticles offer different functionalities such as mucoadhesion, mucopenetration, passive targeting of inflamed tissues in the GI tract, and capture by the immune cells (For review articles on nanoparticles used for IBD, see references[16-22]). On the other hand, polysaccharides exhibit intrinsic biological activity such as anti-inflammatory, healing, immunomodulation, and regulation of the intestinal microbiota (For a review article on polysaccharide-based DDS for IBD, see reference[23].

In this review, we will first discuss the up-to-date knowledge on pathophysiology of IBD and its implication in the design of oral DDS. Physiological changes of the gastro-intestinal tract during active IBD and their implications for designing oral DDS strategies will be underscored. After that, we will analyze the undergoing research strategies using nanoparticles and polysaccharides for IBD. Finally, challenges and perspectives in the oral delivery of nanoparticles and polysaccharides for IBD treatment will be discussed.

1. Overview of the anatomy and physiology of the colon

The colon, or large intestine, constitutes the final part of the GI tract. The colon is approximately 150 cm in length and is divided into six main segments.[24] The first segment is the coecum, where the colon connects to the small intestine. Then comes the ascending colon, the transverse colon, the descending colon, the sigmoid colon, and finally the rectum. The appendix is another part of the colon connected to the coecum. Studies identified it as a component of the immune system.[25] From a histological point of view, the colon comprises four layers. The outermost layer that overlooks the intestinal lumen is the mucosa, then comes the sub-mucosa, the muscularis, and finally the serosa.[26] Above the colon tissue lays a thick mucus layer involved in food digestion, immunity, and protects the GI tract from virulent microbes for example. On the top of the mucus layer lay millions of bacteria which constitute the gut microbiota.[27]

Colon histology revealed that its epithelium is arranged in crypts, where different cells are unequally distributed.[28] In the basement of the crypts lays the stem cells that differentiate while migrating up in the crypts to mainly four different types of functional cells (Figure 1).[29] Enterocytes represent the most abundant cells in the colon epithelium (Figure 1). They are responsible for nutrient absorption. Goblet cells are responsible for mucus secretion. Enteroendocrine cells are involved in the secretion of GI hormones. Paneth cells oversee the secretion of antimicrobial peptides in the colon's lumen. Antimicrobial peptides protect the colon microenvironment from bacteria, viruses, fungi, and even cancerous cells. Antimicrobial peptides play a role in immunomodulation and actively participate in the immune system.[30] Microfold cells (M cells) are other types of cells. They are mainly distributed in the small intestine but can be found in the colon in the gut-associated lymphoid tissue (GALT) of the Peyer's patches.

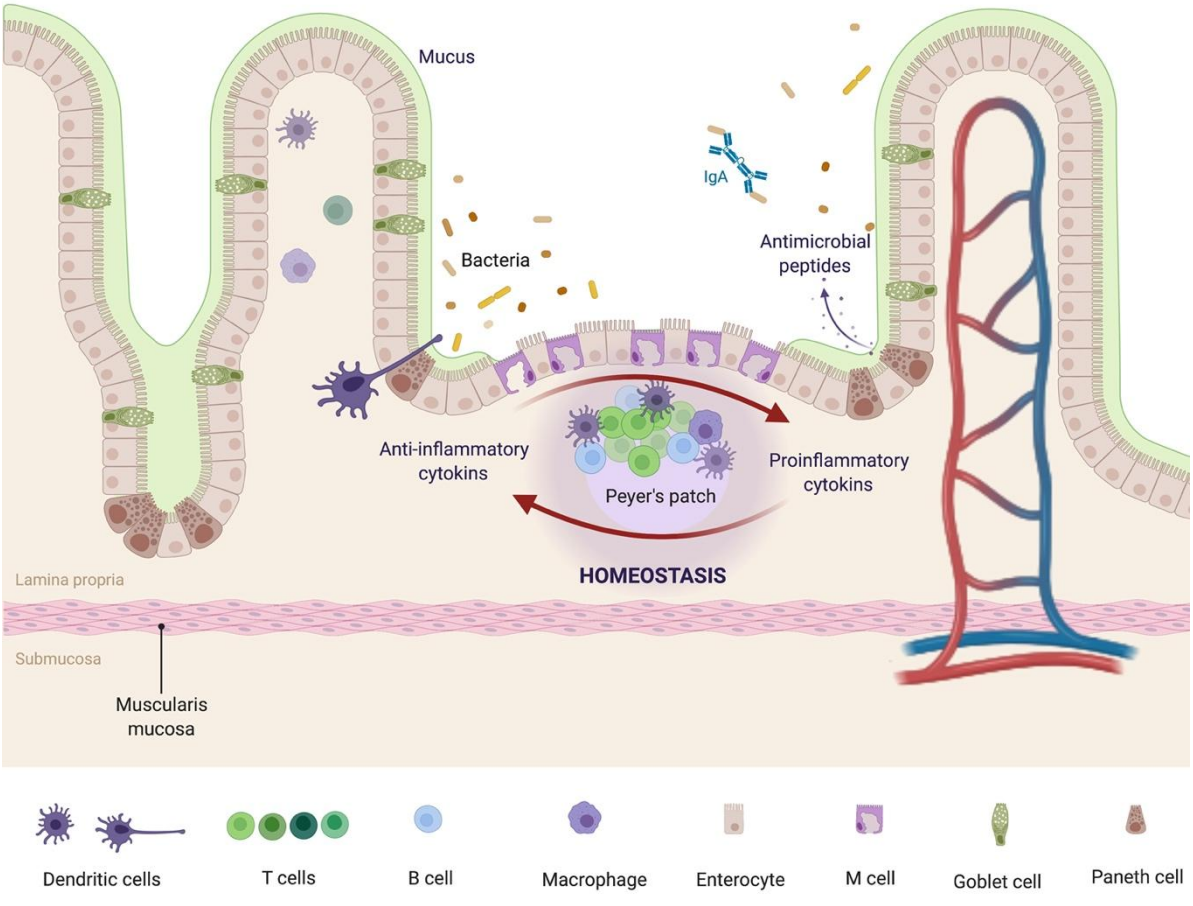

Figure 1: Scheme summarizing the anatomy and physiology in the intestine during a homeostasic state.

2. Pathophysiology and complications of IBD

The pathophysiology of both UC and CD is not clearly elucidated. At the same time, many gaps toward the comprehension of these diseases have been filled in the last years. These fundamental findings opened new avenues for accelerating the race toward developing new therapeutic protocols. One of the most studied areas in IBD relies on the factors predisposing its development. These triggers could be either genetic or environmental, as it is described in Table 1. Following an exposition to one of the previously described genetic or environmental triggers, the microbial peptides that are typically secreted in the intestinal lumen translocate in the lamina propria, either through dysfunction of M cells or because of an impaired barrier function (Figure 2). The barriers' function impairment also allows the translocation of luminal bacteria into the lamina propria.[31, 32] The translocated bacteria activate the professional immune cells (e.g., dendritic cells, macrophages) that engulf the pathogens and present their epitopes to CD4 T-cells. Once activated, both CD4 T-cells and professional immune cells start releasing proinflammatory cytokines that trigger the local and systemic complications of IBD (Figure 2). Each cytokine is involved in the inflammatory response by modulating one or more specific functions. Table 2 briefly summarizes the mechanism of action of the main cytokines implicated in IBD.

IBD can trigger both local and systemic complications. Local complications are a consequence of the epithelial cells swelling and may differ according to the type of pathology. UC and CD share some similar local complications such as blood or mucus in the stool,[33] perforation of the bowel,[34] predisposition to colon cancer,[35] and loss of body weight[36] due to the disruption of reabsorption of water and nutrients by the intestine. However, there are some other complications that are typical for each pathology. During a CD episode, the patient may also encounter an abscess formation,[37] fistula,[38] a lymph adenopathy,[39] and bowel wall obstruction.[40] During a UC episode, one can observe a toxic megacolon[41] as well as a loss of haustra form.[42] The high proinflammatory cytokines level in the blood during the active phase of IBD is responsible for the various systemic complications such as conjunctivitis,[43] mouth ulcer,[44] the presence of an abscess in the liver,[45] portal vein thrombosis,[46] large joint arthritis,[47] and pyoderma gangrenosum.[48]

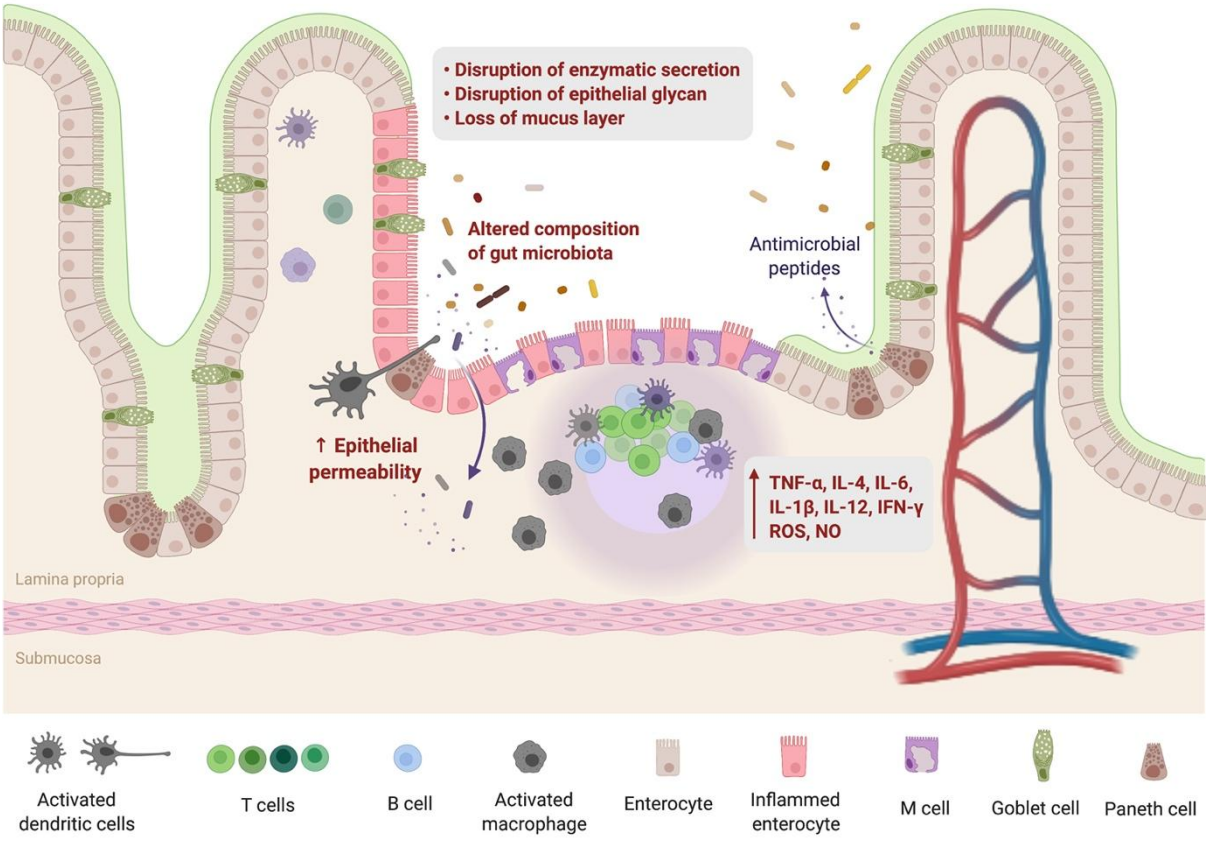

Figure 2: Pathophysiological process and cytokines productions during an IBD.

1 *Table 1: Review of the genetic and environmental factors implicated in IBD.*

Factors	Expression	Pathophysiology	Ref
Genetic factors	Autophagic dysfunction	Many autophagy gene variants were linked to IBD, among which *ATG16L1* (promotes autophagosome formation and participates in suppressing Paneth cells) and IRGM (responsible for phagosome maturation).	[49]
	Cytokine imbalance	Cytokines are essential in the modulation of the intestinal immune system. During an IBD episode, there is an imbalance between pro and anti-inflammatory cytokines, which favor the progress of the proinflammatory process.	[50, 51]
	Bacterial imbalance	During an IBD episode, bacterial dysbiosis occurs mainly in mucosal samples. In that regard, an increase in the abundance of certain types of bacteria (e.g., *Enterobacteriaceae*., *Pasteurellacaea*, and *Veillonellaceae*) was noticed, accompanied by a decrease of other types (e.g., Erysipelotrichales, Bacteroidales, and Clostridiales).	[52]
Environmental factors	Diet	The dietary habits influence the gut fatty acids equilibrium, modifying many parameters such as the pro and anti-inflammatory cytokines balance, the gut microbiota, and the intestinal permeability. For example, a study highlighted that a Mediterranean diet is less likely to induce colitis than a western diet.	[53, 54]
	Stress	The role of the brain-gut axis in the induction of colitis was more recently studied than other factors. During a stress episode, hypothalamic secretion of corticotrophin-releasing factor (CRF) influences the secretion of cortisol by the adrenal cortex. High cortisol levels are involved in IBD by disrupting the gut microbiota, damaging intestinal barrier function.	[11, 55]
	Non-steroids anti-inflammatory	Prostaglandins play a crucial role in the mucosal and immune defenses in the colon. During the therapy, there is selective inhibition of COX1 and COX2 receptors. These two receptors are implicated in prostaglandin production. Low levels of prostaglandins are correlated to the development or the exacerbation of colitis.	[56, 57]
	Smoking	Cigarette smoke plays an important role in colorectal neoplasia development in IBD patients. Furthermore, smoking significantly increases the risk of developing and worsens CD.	[58-60]
	Antibiotic	Antibiotics favor the development of IBD through several mechanisms. They can alter the gut microbiome balance, favoring the intestinal proinflammatory phenotype. Studies reported that developing IBD is antibiotic dose-dependent, with a higher prevalence while using board-spectrum antibiotics. From another standpoint, certain antibiotics such as ciprofloxacin or rifaximin also favor remission from an IBD by targeting specific bacteria linked with the progression of the inflammation.	[61, 62]

Table 2: Main cytokines involved during an IBD episode.

Cytokine	Mechanism of action
TNF-α	TNF-α is a significant cytokine produced mainly by $CD14^+$ macrophages. TNF-α plays a significant role in the pathogenesis of both UC and CD. Binding to NTF-a receptors (TNFR1 and TNFR2) activated the nuclear factor-κB (NF-κB) family, which plays a significant role in the regulation of genes involved in inflammation.[63, 64]
IL-6	IL-6 is secreted mainly by macrophages but can also be produced by $CD4^+$ T cells.[65, 66] Intestinal inflammation is induced following the interaction of IL-6 with membrane glycoprotein (gp130) on the surface of CD4 T-cells.[67, 68] IL-6 also plays a homeostatic role as it promotes the proliferation of intestinal epithelial cells.[69]
IL-1	During the active phase of IBD, lamina propria dendritic cells and macrophages, in addition to endothelial cells, increase the production of IL-1 cytokines. There are three subtypes of IL-1 cytokines, two agonistic proteins (IL-1α, IL-1β), which favor inflammation, and one antagonistic protein (IL1-Ra) that reduces the inflammatory response.[70] Although their mechanism of action is not clearly elucidated; it was shown in several studies that this higher production of IL-1 cytokines during IBD induces an imbalance between IL-1 agonists and their natural antagonist,[71-73] which favors the progress of the inflammation in the colon.
IL-12	IL-12 cytokine family is mainly produced by dendritic cells and macrophages. IL-12 participates in the progress of inflammation after binding to its receptors (IL-12R-β2). IL-12R-β2 are overexpressed during inflammation by the T cells in the mucosa and the lamina propria. Accordingly, their stimulation favors a Th1 immune response, thus promoting mucosal degradation and lamina propria expansion. In addition to Th1 activation, IL-12 stimulates innate lymphoid cells (ILCs) to produce IFN-γ, as recent studies demonstrated that inhibiting IL-12 results in a lower production of IFN-γ during a CD episode.[74] IL-23 binds its receptor (a combination of IL-12R β1 and IL-23R[75]) and induces the formation of Th17 cells out of their naïve CD4+ T counterparts.[76] Th17 cells have both biochemical role by the further induction of proinflammatory cytokines (IL-17, TNF-α, and IL-6),[77] and an immunological role by promoting the activation of CD8+ T,[78] natural killer (NK)[79] and ILCs[80]
IFN-γ	IFN-γ is mainly produced by T_H1-cells of the lamina propria,[81, 82] but also by NK cells. Its level increased during IBD.[83, 84] Also, it stimulates macrophages to produce proinflammatory cytokines.[85] It was recently reported that IFN-γ worsen the pathogenesis of IBD by breaking down the vascular barrier while targeting adherents junction protein VE-cadherin.[86]
IL-4	IL-4 is a cytokine primarily produced by T_H2 cells. Although lack of understanding of the activity of IL-4, it is known that IL-4 plays a role in promoting B-cells and T-cells. IL-4 also has a well-documented immunosuppressive effect in the intestine.[50] Other studies depicted the role of IL-4 in the inhibition of vascular endothelial growth factor during IBD.[87]
IL-13	IL-13 is another T_H2-related cytokine. During UC, IL-13 is implicated in the aggravation of the pathology as it impairs the epithelial barrier function while affecting the tight junctions and inducing epithelial apoptosis.[88] It is also reported in another study that tissue fibrosis occurrence is correlated to the binding of IL-13 with a novel

	cell surface receptor IL-13α.[89]
IL-17	IL-17 is a proinflammatory cytokine exclusively produced by T-lymphocytes (CD45RO+ cells).[90] During an inflammatory process, IL-17 further stimulates the secretion of characteristic proinflammatory cytokines such as IL-1β and TNF-α.[91]
TGF-β	TGF-β is secreted by lymphoid and non-lymphoid cells[92, 93] (e.g., macrophages, fibroblast, epithelial cells). It is synthesized in an inactive form which is activated after binding latency-associated peptides. TGF-β plays a crucial regulatory role in the immune system while controlling the production of several immune systems. On the one hand, they promote the proliferation of regulatory T cells (Treg),[94] favoring the production of anti-inflammatory cytokines (e.g., IL-10). On the other hand, they participate in the neutralization of pathogens by promoting the generation and maturation of IgA producing B-cells[95] and boosting the activity of dendritic cells and macrophages.[96, 97]
IL-10	IL-10 is an anti-inflammatory cytokine. It is produced primarily by monocytes. It monitors IBD by the inhibition of proinflammatory cytokines production by T_H1 cells. Other studies reported that, following a bacterial invasion, IL-10 expresses an inhibitory effect on the secretion of proinflammatory cytokines by Toll-like receptor-triggered myeloid lineage cells.[98, 99]

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Table 3: Current therapeutic protocols for the monitoring of UC and CD.

	UC	**CD**	**Ref**
Active phase	During an extensive UC: - Oral 5-ASA - Oral corticosteroids During a severe UC: - Rehydration - intravenous corticosteroids - intravenous antibiotics - TNF-α antagonist (anti- TNF-α) - Surgery	Adjusting diet: - A fibber rich meal - Avoiding excess proteins During a severe CD: - Corticosteroids - Immunosuppression - Surgery (less favorable due to the non-continuous character of CD) - TNF-α antagonist for chronic patients	[100]
Cold phase	Maintenance protocol consists of: - Oral 5-ASA therapy	Maintenance protocol aims at reducing the immune response: - Thiopurine - Methotrexate	

3. General overview of conventional therapeutic agents for IBD and their shortcomings

The management of IBD aims to treat the acute attacks during the inflammatory process or prevent it from recurring during the cold phase of the disease. Depending on the type of IBD, the therapeutic protocol is different, as illustrated in table 3. For several years, the standard treatment consisted of administering steroids anti-inflammatory, immunomodulators such as thiopurines and methotrexate, cyclosporine, aminosalicylates (e.g., 5-ASA), and surgery by removing the damaged section of the intestine.

5-ASA exerts its effect through antioxidant activity and modulation of inflammatory mediators. Unfortunately, the use of 5-ASA is linked to diverse side effects (e.g., fever, nausea, diarrhea, cramping, headaches, rashes, and in some cases, hair loss, nephritis, pancreatitis, and pancytopenia). 5-ASA is rapidly absorbed from the small intestine leading to low local availability in the colon. It is thus necessary to formulate 5-ASA in adequate DDS to increase local bioavailability, lower applicable 5-ASA doses, and decrease side effects.

Corticosteroids are another standard drug class used in IBD patients. Although corticosteroids provide a robust anti-inflammatory response, their use is commonly related to strong side effects that arise only a few weeks following the start of a topical or systemic treatment.[101-104] Those side effects (e.g., Cushing's syndrome, infection, adrenal suppression, sleep disorders, osteoporosis, and renal function impairment) limit their application in long-term therapy. Recent endeavors suggest that using nanoparticles to deliver corticosteroids during an IBD allows keeping their steroid anti-inflammatory response while minimizing the systemic side effects by targeted delivery of the API into the inflamed colon. From another perspective, certain corticosteroids (e.g., budesonide) have a low mucus penetrating capability, justifying the use of nanoparticles to enhance their penetrability.[105]

Immunosuppressants can target specific proteins in the body that induce inflammation. Monoclonal antibodies targeting specific cytokines were used to monitor IBD. Indeed, anti-TNF-α (e.g., infliximab, adalimumab, golimumab) constitute the mainstream of biological treatment during the active phase of IBD and as maintenance therapy.[106] Also, anti-IL-12 (e.g., ustekinumab) is used only in the case of CD.[107] One major drawback of biologics protocol is the primary nonresponse or a loss of response during treatments. The best example would be anti-TNF-α based therapy, where 30% of the patients present a primary nonresponse,[108] while 30 to 50% lost the response over time.[109] Up to date, many biological-

based therapeutics are available in the market (e.g., certolizumab, infliximab, adalimumab, natalizumab, vedolizumab). Nonetheless, the administration of biologics is commonly applied by the parenteral routes (e.g., subcutaneous, intramuscular, or intravenous), and their long-lasting use is associated with numerous side effects such as immunosuppression,[110-113] infection,[114] cancer,[115] and the formation of antibodies against biologics, reducing their efficacy. Consequently, a novel drug delivery strategy relying on nanoparticles has been more and more investigated in the last year to administrate the API orally, besides reducing their dose through a more targeted delivery to the inflamed regions.[116-118]

Using nanoparticles for the oral delivery of immunosuppressants to IBD patients is a promising approach to reduce their side effects. Indeed, monitoring the aberrant balance of the immune system during UC or CD relies on controlling various immune cells, enzymes, and cytokines through the administration of immunosuppressants (e.g., methotrexate, cyclosporine A, tacrolimus). However, their poor solubility often limits their performance,[119-121] urging to increase the administered dose. Also, misusing these therapeutic agents and systemic administration led to off-target severe side effects (e.g., immunodeficiency, allergies, a loss of activity following a long systemic circulation). Nanoparticle development offers the possibility of selectively targeting the colon's inflamed region and a controlled release of the immunosuppressant.[122] They also play a role in protecting the drugs from degradation during their journey in the GI tract.[123, 124] Table 4 summarizes the significant works in designing nanoparticle-based IBD therapy.

4. Implication of pathophysiological changes of the GI tract during active IBD for oral drug delivery strategies

Active IBD could induce several changes in the GI tract barriers that should be fully understood and considered for developing efficient DDS and identifying therapeutic targets.[125-127] Those changes concern the pH, degradative enzymes,[127] mucus barrier function, microbiota composition[20, 128] and the permeability of the intestinal epithelium.[129]

4.1. pH changes

In healthy subjects, the stomach pH ranges from 1.0 to 2.5 (fasted). It rises from 6.6 to 7.5 in the small and the large intestine. More precisely, luminal pH in the proximal small bowel ranges from $5.5 - 7.0$ and gradually rises to $6.5 - 7.5$ in the distal ileum. In the caecum, the pH decreases to $5.5 - 7.5$ and rises from 6.87 in the proximal colon to 7.2 in the distal colon. In UC and CD patients, the pH of the stomach was found higher than in healthy subjects.[130] This change was correlated to a decrease in the acidic secretions of the stomach. In UC and CD patients, no significant changes in the pH of the small intestine were reported compared to healthy subjects.[130-132] Although the colonic pH of patients with IBD broadly fluctuates depending on the individuals and the disease state, patients are generally subject to acidic pH in the colon.[133, 134] The pH in UC and CD patients ranged from 5.5 to as low as 2.3.[133, 135, 136] The decrease in the colonic pH is due to disruption of factors including intestinal volume, transit time, microbial fermentation, bile acid metabolism of fatty acids, bicarbonate, and lactate secretions.[134] Changes in colonic pH in UC and CD patients could affect the composition of the microbiome and consequently the colonic transit. The residence time of the drugs in the colon, drug release, and absorption are thus modified. Additionally, pH changes could affect drug release from pH-sensitive formulations.

The pH change along the GI tract was exploited to design DDS able to disintegrate at a specific pH range to release the API. A general strategy consists in coating the DDS with polymers that are pH-sensitive. Polymers used for colon delivery are methacrylic acid, polymethacrylic acid, polyacrylic acid, and their derivatives which respond to the high pH of the colon (≥ 6.8).[19] So far, the most common pH-sensitive systems for oral drug delivery in IBD treatment are composed of methacrylic acid co-polymers (Eudragit®). Eudragit S100 (ES100), which should dissolve in the distal intestine at a pH of 7, is the most used polymer for colon drug delivery. ES100-containing DDS exhibited pH-sensitive properties by limiting the burst release at the gastric pH. Most of the drug was released at pH higher than 7.[137, 138]

The pH at which the drug is released could be adjusted to lower values by mixing ES100 to other methacrylic acid co-polymers that dissolve at low pH.[139] Eudragit L100 is soluble at pH 6, while EL30-D55 was used to manipulate the drug release within the desired pH range of $5.5-7.0$ in the distal small intestine. The appropriate colon dissolution pH of delivery systems can be controlled by optimizing the ratio of EL30-D55 and ES100 for targeted drug delivery to the inflamed colon.[139] More recently, coating nanoparticulate DDS with Eudragit FS 30D conferred a sustained release of the encapsulated drugs.[140] Indeed, Eudragit FS 30D dissolves similarly to Eudragit S100 at pH 7 but in a more sustained and controlled mode. The Eudragit-coated strategy of nanoparticulate DDS was applied for many types of nanostructures,[19] including polymer,[141] lipidic,[142] polysaccharide-based,[143] or inorganic nanoparticles.[138]

Other types of pH-sensitive materials were used for designing nanoparticles that can target and remain in the inflamed colonic tissue through multiple mechanisms. Hybrid nanoparticles composed of pH and enzyme-sensitive polymers were designed by combining ES100 and azopolyurethane polymers.[144, 145] However, as mentioned above, the colonic pH in patients with IBD could be more acidic than in healthy subjects. Consequently, the DDS coated with Eudragit that dissolves at pH higher than 6 might not release the drug in vivo. Indeed, in most investigations on Eudragit-based nanoparticles, the drug release was evaluated in vitro in simulated colonic media without mimicking IBD disorders. In the next section, we will discuss the interest of polysaccharides for designing pH-sensitive DDS that could be an alternative to synthetic polymers.

4.2. Mucus

In healthy subjects, mucus is a viscoelastic hydrogel composed of water ($90-98$ wt%), mucins ($2-5$ wt%), lipids ($1-2$ wt% primarily associated with hydrophobic domains of mucin glycoproteins), mineral salts (2 wt%), and proteins (immunoglobulins A and M, lysozyme) that contribute to the mucus elasticity.[146, 147] The degree of mucus hydration is a significant determinant of mucus viscoelasticity. Mucin fibers (typically $10-40$ MDa, $3-10$ nm in diameter)[148] are crosslinked and entangled macromolecules secreted by both goblet cells and the seromucinous glands of the lamina propria at the apical epithelium.[149] Mucins are proteins glycosylated by *O*-linked *N*-acetyl galactosamine and *N*-linked sulfate-bearing glycans.[150] Dense glycan coverage of mucins represents up to 80% of the dry weight of mucus. For 100 amino acid residues, carbohydrate chains represent $25-30$,[151] and contribute up to 80% of the dry weight of mucus (For review articles on mucus, see

references[152-154]). The glycocalyx that protects cell surfaces comprises cell-associated mucins and mucus gels formed by secreted gel-forming mucins.[153]

Significant changes in mucus composition, thickness, physical properties, and function were reported in IBD. CD is characterized by goblet cell hypertrophy, while patients with UC are characterized by a reduction and depletion of goblet cells. In this latter case, mucus production is significantly decreased, and the thickness of mucus layers was reduced in the colon and the rectum.[155, 156] In UC, the substantial increase in mucus production leads to a thicker mucus layer in the inflamed areas. Consequently, a higher amount of nanoparticle adherence was reported for inflamed areas compared to healthy mucosa. Due to their small size, nanoparticles were better retained in the intestinal tract than large particles. Smaller nanoparticles are known to exhibit better mucoadhesion and mucopenetration compared to larger particles.[157, 158] Lamprecht et al.,[159] demonstrated an inverse relationship between particle size and binding to the inflamed intestinal mucosa. They revealed that particles smaller than 100 nm exhibited the highest binding affinity to inflamed colonic tissue. The reduction of the DDS size to the nanometer scale improved colonic residence time in inflamed regions of the intestine and provided benefits for IBD treatment. Particles with a size larger than 200 μm are subjected to diarrhea symptoms, resulting in a decreased GI transit time and, therefore, decreased efficiency.[160, 161]

PEGylation strategy improves mucopenetration properties of nanoparticles. Being hydrophilic and uncharged, the presence of poly(ethylene glycol) (PEG) confers to nanoparticulate DDS mucus penetrating properties.[157, 162-164] The behaviors of PEG nano-delivery systems toward mucus are dependent on the molecular weight. Low PEG molecular weight (2-5 kDa) provided a non-mucoadhesive coating on nanoparticles. Whereas coatings using 10 kDa PEG resulted in strong particle mucoadhesion.[163, 164] The surface charge of PEGylated nanoparticles showed a significant impact on their accumulation in the inflamed colon of a dextran sulfate sodium (DSS)-induced mice model of acute UC.[165] Nanoparticles had a 100-nm diameter and were composed of poly(ethylene glycol)$_{5k}$-*b*-poly(lactic-co-glycolic acid)$_{10k}$ (PEG$_{5k}$-*b*-PLGA$_{10k}$). They were loaded with TNF-α siRNA.[165] In this study, cationic PEGylated PLGA nanoparticles showed a higher accumulation in the colon and a better silencing capacity than nanoparticles with a neutral charge.

In patients with active UC, the carbohydrate content of the epithelial glycan, including mucus glycoproteins, is altered compared with healthy controls (For reviews on epithelial glycans in IBD, see references[166-168]). Epithelial glycans are a major component of the

intestinal mucosa. Glycans typically form glycoconjugates (e.g., glycoproteins and glycolipids) by attaching to other molecules (e.g., cytosolic lipids or membrane-associated lipids and proteins). Thanks to their position at the interface between the epithelial cells and the outer mucus layer, glycans serve as attachment sites for nutrients and ligand-binding proteins (e.g., antibodies, lectins). They also play an essential role in the interaction between intestinal epithelia and the commensal flora in the mucus. The major class of glycan in the gut (80 wt% of MUC2) is composed of mucin-type O-glycans.

In patients with active disease, intestinal epithelial glycosylation is disrupted.[167-169] Alterations include truncated mucin-type O-glycans and a reduction of oligosaccharide chain length and sulfatation, conferring less negative charge to mucins.[169, 170] Reduced sulfatation was correlated to increased activity of mucin sulfatase. Structural and immunohistochemical studies revealed that patients with active IBD were characterized by a simplified O-glycome.[171] The amount of smaller glycans was increased, while more complex structures were lowered. Glycan disruption altered intestinal immunity, disrupted glycan-lectin and host-microorganism interactions, and altered MUC2 synthesis[168] and stability. Glycome simplification makes mucins more accessible to host and bacterial proteases.[172] The loss of mucus viscoelasticity and reduction of barrier properties lead to enhanced interactions of bacteria and intestinal epithelia. Furthermore, a significant correlation was found between changes in glycosylation and the level of inflammation.[169]

Understanding the disorders of epithelial glycosylation in IBD patients with active disease is fundamental for developing strategies for 'remodeling' the disease-associated glycan by targeting intestinal epithelial glycosylation. Those approaches include direct methods (e.g., inhibitors of glycosidases,[173] or sulfatases[174, 175]) and indirect methods (e.g., normalizing the gut microbiota by faecal transplantation or prebiotics, or by bacterial products). Inhibiting protein-glycan interactions that contribute to recruiting pathogenic bacteria or inflammatory cells seems to be a promising strategy to alleviate inflammation in IBD patients.[168] For example, galactose interferes with the interaction of *Fusobacterium nucleatum* (a Gram-negative commensal bacteria) with the carbohydrate epitope galactose or *N*-acetyl-galactosamine (Gal, GalNAc).[176, 177] It was found that the interaction of *F. nucleatum* Fap-2 (fibroblast activation protein 2), and Gal or GalNAc was implicated in numerous diseases, including IBD and cancer.[178] These findings should trigger further investigations to design DDS to block Fap-2/Gal or Fap-2/GalNAc interaction. Similarly, it was demonstrated that blocking the interaction of *Escherichia coli* FimH lectin with epithelial glycan prevents

mucosal inflammation associated with CD.[179] Knowing that mannose derivates are able to interact with FimH, several research works were dedicated to developing mannose derivatives to alleviate inflammation. Interestingly, the FimH blocker Sibofimloc (EB8018/TAK-018) derived from the patent WO2014100158A1 has entered the clinical trials for CD.[180] Thanks to safety and pharmacokinetic results obtained in 2020,[180] the clinical development program is continuing with a phase 2 trial in patients with CD.

On the other hand, ulcerated tissues contain high concentrations of positively charged proteins that increase the affinity to negatively charged substances.[181] In particular, inflamed colon contains high concentrations of transferrin and eosinophil cationic protein.[182-185] This property was exploited in designing negatively charged DDS that preferentially adhered inflamed tissue *in vivo* through electrostatic interactions with positively charged proteins.[159, 186, 187] However, conflicting results were obtained in the literature on the impact of nanoparticle charge on their accumulation in the inflamed colon since the net charge of mucus remains negative due to the presence of mucins. Iqbal et al.,[165] revealed that cationic nanoparticles exhibited remarkably higher accumulation in the inflamed colon compared to anionic nanoparticles.[165]

4.3. Enzymatic secretions

In CD patients, the enzymatic secretion was significantly modified in comparison with healthy subjects. Indeed, for digestive purposes, the lumen of the upper GI tract contains large amounts of pancreatic proteases, but studies have also demonstrated increased proteolytic activity into mucosal tissues (both in the upper and lower GI tract), associated with pathological conditions such as IBD. This upregulation was correlated with the degradation of tight junctions.[188] In that context, protease inhibition was used as a therapeutic approach in IBD treatment.[188] Additionally, increased fluid secretion can dilute the digestive enzymes implicated in intestinal transit.

4.4. Epithelial barrier

As detailed above, in IBD patients, the intestinal epithelium is characterized by epithelial defects, including a loss of continuous epithelium,[189] TNF-α mediated epithelial apoptosis in the colon,[190] and damage of epithelial thigh junctions. In particular, abnormal expression of tight junction proteins (e.g., occluding, ZO-1 and claudins)[191] is an essential characteristic in IBD. They lead to increased permeability of colonic epithelial mucosa and a loss of the barrier function of the mucosa toward microbes, toxic substances such as lipoproteins, causing

inflammatory response. A consequence of epithelial shedding and impaired paracellular epithelial barrier in IBD was exploited by different research groups to passively target API and nanoparticles to the inflamed tissue through the so-called epithelial enhanced permeability and retention (eEPR) effect. A study implied that the recurrence of budesonide-loaded PLGA/Eudragit nanoparticles improved the anti-inflammatory effect of budesonide.[192] The authors suggest that these observations could be linked to the high adhesion and uptake of the nanoparticles mediated by the eEPR effect, which increased the levels of budesonides in the inflamed site.

In a more recent investigation, Ahmad et al.[193] used polycaprolactone (PCL) covalently grafted with aminocellulose and used to prepare nanoparticles loaded with anti-inflammatory drugs (e.g., glycyrrhizic acid, budesonide). Nanoparticles designed by solvent evaporation had a mean hydrodynamic diameter of ~230 nm and positive zeta potential (24 to 29 mV). This study revealed that nanoparticles had a preferential accumulation in the inflamed colon in mice with DSS-induced colitis. Higher accumulation in the inflamed colon could be due to passive targeting by eEPR since no accumulation of nanoparticles in a healthy colon was reported.[193] These nanoparticles improved disease activities like occult blood in the stool, length of the colon, and fecal properties. Also, the nanoparticles decreased colonic mast cellular infiltration, significantly maintained mucin protection, improved histological features of the colon, and ameliorated the markers of inflammation (e.g., induced nitric oxide (NO) synthetase (iNOS), cyclooxygenase (COX)-2, IL1-β, TNF-α, and myeloperoxidase (MPO)).[193]

4.5. Modifications of immune cell surface receptors

In inflamed tissues, the immune cells are subject to different modifications of the expression of cell receptors. In the inflamed state of UC, the glycoprotein CD98 is overexpressed by colonic epithelial cells and macrophages. CD44 receptor is another glycoprotein overexpressed on the activated inflammatory cells in colitis tissues. Active targeting by nanoparticulate DDS consists of the intentional orientation of the localization of nanoparticles to inflamed tissues.[194, 195] This results from a high concentration of nanoparticles in the disease site and consequently high therapeutic efficacy of a drug, while the adverse effects on normal tissue are reduced.[195, 196]

Another strategy targets receptors naturally expressed by macrophages and dendritic cells. Because macrophages and dendritic cells are abundant in inflamed tissues, targeting receptors

Table 4: Table summarizing the recent work on the use of nanoparticles for alleviating IBD.

(e.g., dectin-1, galactose agglutinin, and mannose receptor) promoted the distribution of targeted nanoparticles in the inflamed tissues.[197-201] The ligands that can target receptors on macrophages include saccharides (e.g., mannose,[198-200] hyaluronan, galactose[201]), dectin-1 able to recognize β-glucan, lectins, or monoclonal antibodies.

4.6. Production of reactive oxygen species

In response to inflammatory stimuli through specialized enzyme complexes called NADPH oxidase, reactive oxygen species (ROS) can be produced by epithelial cells and innate immune cells, including resident monocytes/macrophages, dendritic cells, or infiltrated neutrophils. Those cells are able to produce ROS into the mucus and intestinal lumen.[202] The intestinal mucosa of patients with IBD is characterized by severe disorders of antioxidants and ROS overexpression by immune cells (e.g., neutrophils and macrophages), leading to oxidative damage. ROS concentration was up to 100-fold higher than in control patients.[203] In this context, several researchers exploited this property to design ROS-scavenger DDS able to reduce oxidative stress and inflammatory response. Those strategies include colon-targeted delivery of nanoparticles containing donors of NO radicals (e.g., NO-nitrosothiols) or antioxidant molecules (e.g., bilirubin, curcumin, ginger, resveratrol).

API	Materials composing the nanoparticles	Inflammation model	Delivery route	Observations	Ref
Corticosteroids (budesonide)	PLGA/ Eudragit S100	Trinitrobenzosulfonic acid (TNBS) (mice) DSS (mice) Oxazolone (mice)	Oral	Comparing budesonide-loaded nanoparticles to the free drug revealed: - A better histological, biological, and endoscopic data regarding inflammation reduction while using nanoparticles. - Nanoparticles could be tuned into pH-responsive nanosystems allowing targeted delivery, considering the acidic pH environment of the inflamed area.	141
Corticosteroids (Budesonide)	PLGA and Eudragit S100	TNBS (rats)	Oral	- Budesonide-loaded nanospheres had a higher impact on the reduction of TNBS induced colitis. - The inflammation reduction could be linked to the inflamed mucosa's higher systemic availability and cellular uptake of nanospheres.	192
Corticosteroids (Budesonide)	Mannosylated nanostructured lipid carrier system (Mn-NLCs)	Oxazolone (mice)	Oral	The in vivo data following the administration of a budesonide-loaded Mn-NLCs and a budesonide suspension revealed: - A lower clinical, macroscopic, and microscopic scoring with the budesonide Mn-NLCs treated group. - A lower level of proinflammatory cytokines and myeloperoxidase.	204
Corticosteroids (Prednisolone)	ε- polylysine-coated mesoporous silica	RAW 264 cells Caco-2 cells	NA	- A high inhibition of inflammation was observed at the cellular level.	205
Corticosteroids (Betamethasone)	Lectin-conjugated PLGA	TNBS (mice)	Oral	- Lectin-decorated PLGA-nanoparticles selectivity increased adhesion to inflamed tissue compared to plain nanoparticles, thus improving their therapeutic effect.	206
5-ASA (Mesalasine)	Polycaprolactone	TNBS (mice)	Oral	- A higher therapeutic effect of encapsulated 5-ASA was observed compared to the free drug.	207
5-ASA (Mesalasine)	Silica	TNBS (mice)	Oral	The use of silica nanoparticles to deliver mesalasine allowed to: - Selectively target the inflamed tissue to deliver the API and spare the healthy tissue. - A higher anti-inflammatory effect was obtained with a lower dose of the API.	208

5-ASA	Silicon dioxide (SiO_2)	DSS (mice)	Oral	- A lower inflammation score was observed with the groups treated by the nanoparticles or with high doses of 5-ASA. - Myeloperoxidase and cytokines (TNF-α and IL-6) levels were also much lower with the 5-ASA-nanoparticles treated group suggesting a higher colon-targeting efficacy of 5-ASA-nanoparticles.	[209]
5-ASA (Mesalasine) Tempol	Redox particles	DSS (mice)	Oral	- Tempol or mesalamine-loaded nanoparticles reduced the inflammation strongly compared with free tempol or mesalasine. - The nanosystems specifically accumulated in the colon during a colitis episode.	[210]
Tempol	Methoxy-poly(ethylene glycol)-b-poly [4-(2,2,6,6-tetramethylpiperidine-1-oxyl)oxymethylstyrene] (MeO-PEG-*b*-PMOT) block copolymer s	DSS (mice)	Oral	- Following a DSS-induced inflammation, an increase of commensal bacteria (*Escherichia coli*, *Staphylococcus spp.*) was noticed. - The nanoparticle administration reduced the prevalence of these commensal bacteria.	[211]
Biologics (Anti-TNF-α)	Natural polyphenol tannic acid and poly(ethylene glycol)	DSS (mice)	Oral	- The oral administration of anti-TNF-α nanoparticles had a significantly higher reduction of inflammation than free anti-TNF-α.	[212]
Biologics (TNF-α siRNA)	Thioketal	DSS (mice)	Oral	- Using thioketal nanoparticles as a carrier to orally deliver siRNA against TNF-α into the colon reduces the TNF-α RNA level in the inflamed region, preventing the worsening of UC.	[213]
Biologics (TNF-α siRNA)	Poly(ethylene glycol)-block-PLGA - Cationic charge: aminated particles - Anionic charge: carboxylate particles - Neutral charge: plain particles	DSS (mice)	Oral	- Aminated nanoparticles expressed the highest accumulation in the colon, translated by increased inhibition of TNF-α secretion and mRNA levels. - Animals treated with aminated nanoparticles had similar histological scores to healthy mice. - The results suggest the significant influence of surface charge on colonic accumulation.	[165]
Biologics (CD98 siRNA)	polyethyleneimine (PEI)	DSS (mice)	Oral	- Significant reduction of colitis occurs through CD98 downregulation in the intestinal	[214]

				epithelial cells.	
Biologics (CD98 siRNA) + Curcumin	PLGA	DSS (mice)	Oral	- PLGA nanoparticles offered a tuneable platform to deliver CD98 siRNA and curcumin in the inflamed colon selectively. - This nanoparticle-based therapy showed promising results in the monitoring of IBD.	[215]
Curcumin	PLGA/Eudragit S100	DSS (mice)	Oral	While compared to groups treated with non-encapsulated curcumin was used, it was noticed: - Decrease of immune cells infiltration. - Reduction of TNF-α levels.	[216]
Curcumin + celecoxib	Eudragit S100	TNBS (mice)	Oral	Eudragit nanoparticles showed the following events: - Targeted delivery to the colon. - Reduced body weight loss and diarrheic stool. - When delivered in a nanoparticulate form, much lower doses of API were needed to obtain the desired effect than a separate administration of drugs.	[217]
Peptides (Lysine-proline-valine) KPV	Alginate and chitosan	DSS (mice)	Oral	KPV-loaded nanoparticles reduced the anti-inflammatory response in DSS pre-treated mice. KPV loaded into nanoparticles can be delivered at a concentration 12,000-fold-lower than a free solution of KPV.	[218]
Immuno-modulator (Rolipram)	PLGA	TNBS (mice)	Oral	- The nanoparticle formulation expressed a similar anti-inflammatory effect to the drug in solution. - Five days post-treatment, the animals that received the nanoparticle formulation showed less relapse than those that received the drug solution. - The animals that received nanoparticle formulation suffered less from the adverse effect caused by rolipram.	[219]
Immuno-modulator (Tacrolimus)	PLGA, Eudragit P-4135F (pH-sensitive)	DSS (mice)	Oral	- Oral tacrolimus-loaded nanoparticles attenuated colitis more efficiently than oral tacrolimus solution. - Lower efficiency of oral tacrolimus-loaded nanoparticles was observed than the drug solution administered subcutaneously. - Encapsulating tacrolimus inside nanoparticles reduced its adverse	[220]

				effect. - Both nanoparticles (PLGA and pH-sensitive Eudragit) showed similar data in reducing colon inflammation. Nonetheless, pH-sensitive nanoparticles were slightly less nephrotoxic.	
Immuno-modulator (Cyclosporine A) CYA	Lipids	DSS (mice)	Oral	- While compared to an oral administration of a commercial solution of Sandimmun (Neoral®), CYA-loaded lipid nanoparticles did not improve the therapeutic effect.	[221]
	PLGA	DSS (mice)	Oral	Compared to drug-free particles and commercial formulation Sandimmun (Neoral®), CYA-loaded PLGA nanoparticle exhibited: - An unchanged body weight. - The concentration of proinflammatory cytokine in the plasma was undetectable. The authors concluded that CYA-loaded PLGA nanoparticles yielded a similar reduction of inflammation at a half dose of the commercial product.	[222]
Immuno-modulator (Methotrexate)	Grapefruit-derived nanovesicles (GDNs)	DSS (mice)	Oral	After their selective internalization by macrophages, GDNs decrease the inflammation by: - Upregulation of heme oxygenase-1 (HO-1) expression. - Inhibition of IL-1β and TNF-α production - Loading methotrexate in GDNs further enhanced their anti-inflammatory property while maintaining the homeostasis of intestinal macrophages.	[223]
Immuno-modulator (Azathioprine)	Chitosan beads	Acetic acid (rabbit)	Oral	Azathioprine has numerous side effects, such as hepatotoxicity, bone marrow suppression, and allergic reaction. The oral administration of Azathioprine-chitosan beads allowed to: - Reduce the systemic side effects of azathioprine. - Decrease the levels of myeloperoxidase and proinflammatory cytokines to the levels of healthy animals. - Restore the microscopic structure of the colon.	[224]
Antibiotics (Rifaximin)	Chitosan	*In vitro*	NA	Encapsulating the drug into chitosan nanoparticles expressed the following	[225]

				data: - Improved the solubility of rifaximin. - Expressed high stability of the formulation. - The formulation offers the possibility of a controlled release of the drug in the targeted region. Nevertheless, *in vivo* investigation still lacks to confirm these observations.	
Probiotic extract	Chitosan-coated PLGA	TNBS (rats)	Oral	- The administration of probiotic extract and nanoparticles significantly mitigated colitis. - The medium dose of probiotic extract-loaded nanoparticles reduced the inflammation more efficiently than the high dose of its free administered counterpart.	[226]
Prohibitin	Ply(lactic acid) (PLA) Adenovirus	DSS (mice)	Oral enema	- Prohibitin has an anti-inflammatory property, but its levels decrease during an IBD episode. - Oral prohibitin-loaded PLA particles or rectal prohibitin-loaded adenovirus increased the prohibitin levels in the inflamed colonic region. - Increased prohibitin levels correlated with decreased inflammation intensity translated by lower clinical and histological scores, reduced myeloperoxidase activity, proinflammatory cytokines, and protein carbonyl content.	[227]
Ginger active compound (6-shogaol)	Poly(lactic-*co*-glycolic acid)/poly(lactic acid)-polyethylene glycol-folic acid PLGA/PLA-PEG-FA	DSS (mice)	Oral	Oral delivery of 6-shogaol loaded into nanoparticles reduced the virulence of the colitis by: - Diminishing the levels of proinflammatory cytokines (TNF-α, IL-6, IL-1β) - Increasing the level of anti-inflammatory factors such as the nuclear factor (erythroid-derived 2)-like 2 (Nrf-2) and HO-1. - Accelerating wound repair	[228]

5. Polysaccharide-based drug delivery systems for IBD

Polysaccharides are naturally produced by animals, plants, microorganisms, fungus, and algae. Among the polysaccharides' diverse intrinsic biological activities (e.g.,

immunomodulatory, anti-inflammatory, regulation of intestinal flora imbalance, and healing properties), their use to alleviate IBD has gained significant interest over the last years.[23, 229] Table 5 summarizes the main polysaccharides studied for their role in IBD modulation. Polysaccharides manage IBD by different mechanisms. From one side, they can regulate the different proinflammatory signalling pathways such as Toll-like receptors (TLR), mitogen-activated protein kinase (MAPK), nuclear factor-κB (NF-κB), and G-protein coupled receptors. On the other side, polysaccharides play a crucial role in the intestinal flora balance. They increase the symbiotic bacteria (e.g., *Lactobacillus*) and decrease the pathogenic bacteria (e.g., *Facklamia*, *Clostridium*, and *Enterococcus* species).[230, 231] Polysaccharide metabolites, known as short-chain fatty acids (SCFAs); can also modulate the homeostasis of the GI tract as several described their role in the inhibition of pathogenic microorganisms.[232-234] Acetic acid, propionic acid, and butyric acid are the main SCFAs. Lactic acid and valeric acid are also metabolites produced by microbial fermentation of undigested carbohydrates and dietary fibers.[235-237] SCFAs decrease the pH of the intestine. They improve the homeostasis of the intestinal flora by inhibiting the growth of pathogenic bacteria and enabling the proliferation of beneficial bacteria.[238] SCFAs also have direct antimicrobial activity against bacterial pathogens by diffusing across the bacterial membrane and reducing the intracellular pH. In particular, butyrate has a positive effect on epithelial integrity and tight junction permeability.[229, 239] Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase[240] and up-regulating the tight junction protein Claudin-1 transcription.[241] Additionally, butyrate increased mRNA expression and protein abundance of claudins-3 and 4 and influenced intracellular ATP concentration in a dose-dependent manner.

From another perspective, it is well documented that several polysaccharides (e.g., dextran, inulin, chondroitin sulfate, cyclodextrin, and hyaluronan) are stable within the stomach and intestinal environment but are degraded in the colon by the colonic bacterial flora.[242, 243] These characteristics have driven scientists to investigate the possibility of using them as drug carriers to deliver API in the inflamed region of the colon selectively. Accordingly, many studies have flourished while formulating different polysaccharide-micro/nanocarriers.[244-248]

The main polysaccharides used for designing nanoparticles for IBD treatment are chitosan, hyaluronic acid, pectins, alginates, and inulin (Table 5).[249] Other polysaccharides for IBD have also been reported, such as xanthan gum and guar gum.[250, 251] Hereafter,

polysaccharide nanoparticles for IBD are summarized, and the structure-activity relationship is discussed.

5.1. Chitosan

Chitosan is obtained by the partial deacetylation of chitin which is mainly derived from the shells of crustaceans such as lobster, shrimp, or crab. It can also be found in fungi and insects. Chitin is the second largest and most abundant polysaccharide in nature after cellulose. It is responsible for maintaining the fungal shape, strength, and cell's structural integrity. Chitosan is a linear heteropolymer composed of β-(1-4) linked *N*-acetyl-D-glucosamine and D-glucosamine. The molecular weight and the degree of acetylation (DA) are essential characteristics of chitosan. The DA of chitosan ($> 50\%$) represents the fraction of *N*-acetyl-D- glucosamine relative to the total number of units. Contrary to chitin ($DA < 50\%$), which is insoluble in aqueous and many organic solvents, chitosan is hydrophilic and soluble in acidic solutions, while the amine groups present on the macromolecule are protonated. Chitosan with low DA and low molecular weight has increased solubility in water.

However, the physicochemical properties of chitosan derived from the deacetylation of chitin from crustaceans are heterogeneous, depending on the raw material source.[252] More recently, chitosan was produced from chitin contained in selected fungi' cell walls and septa. *Ascomycete*s, *Zygomycetes*, *Basidiomycetes*, and *Deuteromycetes*. Chitosan from fungi is characterized by low molecular weight (e.g., 45 kDa)[253] can be directly extracted from the raw material without needing thermal or chemical depolymerization.

Due to its intrinsic anti-inflammatory, healing, and immunomodulatory activity, chitosan is the most cited polysaccharide in developing nanoparticulate DDS for IBD.[249] It is the only cationic polysaccharide used to develop positively charged nanoparticulate DDS. The net positive charge of chitosan nanoparticles confers mucoadhesive properties through the electrostatic interactions with negatively charged mucins.[254] Chitosan interacts with negatively charged proteoglycan on the cell surface. It increases cell permeability by reversibly acting on paracellular and intracellular pathways of epithelial cells.[255, 256] Nanoparticle intrinsic activity was further improved by functionalizing chitosan to natural molecules such as gingerol, used for its anti-inflammatory and antioxidant properties.[257] The nanoparticles composed of chitosan covalently linked to gingerol ($\sim 50 - 78$ nm, -21 mV) were successfully used for the encapsulation and the controlled release of 5-ASA. Although in

vivo evaluations were not yet performed using those nanoparticles, size and charge properties, as well as drug release control, could be favorable in vivo for the treatment of IBD.[257]

Due to its solubility in acidic media, chitosan-based nanoparticles could exhibit a premature release of the drug before reaching the colon. Different strategies were thus envisioned to improve colon-specific drug delivery in IBD. Chemical crosslinking (e.g., glutaraldehyde) or ionic crosslinking (e.g., tripolyphosphate (TPP)) are the most commonly used methods to make chitosan nanoparticles insoluble in acidic media.[258, 259]

Hybrid multifunctional nanoparticles composed of a blend of chitosan and anionic polysaccharides such as alginate[218, 260-264], hyaluronan,[265, 266] pectins,[258] fucoidans,[267, 268] or carboxymethyl starch[269] showed promise to deliver the drug to the colon and to control its release. Ahmed et al.,[258] demonstrated that the administration of taurine encapsulated in chitosan/pectin nanoparticles exerted beneficial effects in induced colitis in rats thanks to their anti-inflammatory and antioxidant activities. The nanoparticles ($\sim$74 nm, 48 mV) were prepared by ionic gelation and crosslinked with sodium TPP. However, at pH 6.4, a burst release was observed after the first 30 min followed by a slower release over 4 h.[258] Coating of nanoparticles composed of chitosan/TPP with Eudragit (FS30D),[140] confers a sustained release and a pH stimulated delivery of the encapsulated active drug in addition to a good accumulation in the colonic region of UC-induced rats.[140] Nanoparticles composed of multilayers of chitosan oligosaccharide, alginate, and Eudragit S100 demonstrated pH-dependent release of dexamethasone with a limited initial burst release in acidic pH. The nanoparticles exhibited significant therapeutic activity in a colitis-induced mouse model.[270]

The chemical grafting of recognition ligands on chitosan nanoparticles further improved the targeting of the immune cells in the inflamed colon. Galactosylated chitosan nanoparticles were mainly used for the encapsulation of TNF-α siRNA or Map4k4 siRNA to increase the cellular uptake by activated macrophages through the galactose-mediated receptor.[201, 271, 272] Major results revealed that galactosylated nanoparticles that have a high binding affinity for siRNA showed enhanced in vivo anti-inflammatory efficacy in a mouse model of UC.[201, 271] To learn more about chitosan nanoparticle-mediated gene therapy strategies for mitigating IBD, see the review of Verma et al.[16]

5.2. Hyaluronan

Hyaluronan (HA), a nonsulfated glycosaminoglycan, is an essential component of the vertebrate extracellular matrix, where it is naturally present at relatively high concentrations

in the extracellular matrix, especially of soft connective tissues (e.g., skin, vitreous humor, synovial fluid, umbilical cord). Viruses and bacteria also produced HA.[273] HA is a linear heteropolysaccharide composed of repeating β-1,4 bond disaccharide units of D-glucuronic acid and *N*-acetyl-D-glucosamine linked together through β-1,3 glycosidic bonds. HA is a polyanionic polysaccharide. The HA molecule is negatively charged when the pH is higher than the pKa of HA carboxyl groups ($3-4$).

HA is implicated in various physiological functions in the intercellular matrix (e.g., homeostasis of water and plasma protein). HA is either anchored firmly in the plasma membrane or bond via HA-specific binding proteins. Among those receptors, called hyaldherins, CD44 is a transmembrane receptor known to play a critical role in inflammation.[274]

HA has a variable molecular weight depending on the source of production. It is highly polydisperse and varies from 2 kDa to $> 6000\ kDa$. The rheological properties of HA are dependent on the HA molecular weight. In water, HA has a semi-flexible structure adopting a worm-like random coil. The radius of gyration, R_g depends on the molecular weight of HA as follows $R_g \approx 1.3\ nm \times M_w^{0.6}$.[275] HA has intrinsic healing and anti-inflammatory properties that rely on the HA molecular weight. While high molecular weight HA (HMw-HA) has anti-inflammatory activity, low molecular weight HA (LMw-HA) activates an innate immune response. Also, the affinity toward hyaldherins such as CD44 and RHAMM (receptor for HA-mediated motility, designated as CD168) was controlled by the Mw of HA in solution or grafted on the particle surface.[276, 277] Surface plasmon resonance experiments revealed that low molecular weight HA nanoparticles (6.4 kDa) exhibited low binding to CD44 receptor, while high molecular weight HA nanoparticles (1500 kDa) had a high binding affinity.[276]

Intensive research investigations were focused on designing HA functionalized nanoparticles as a vehicle for active drugs to alleviate IBD (e.g., bilirubin,[278] Lysine-proline-valine (KPV tripeptide),[279] budesonide,[280, 281] methotrexate[265]). The drug is either encapsulated or covalently linked to HA nanoparticles. It was demonstrated that CD44 overexpression on the surface of inflamed intestinal epithelial cells[281] and proinflammatory macrophages[278] contributed to the accumulation of HA nanoparticles in the inflamed colonic tissue in DSS-induced colitis mice.[278] In addition to the eEPR effect, the glycoside cluster provided by dense HA on nanoparticle surface contributes to higher receptor-mediated interaction with cells.[282] This property was exploited for the intracellular delivery of nucleic

acids. CD44 targeting HA nanoparticles can selectively deliver siRNA (silencing TNF-α or CD98) to peritoneal macrophages leading to downregulation of proinflammatory cytokines.[215]

HA nanoparticles act on the tight junction proteins ZO-1 and occludin-1, which are tight junction-associated proteins that play pivotal roles in gut homeostasis.[279] DSS-colitis mice orally administered with HA nanoparticles covalently linked to bilirubin normalized the expression patterns and messenger RNA levels of ZO-1 and occludin-1, while other control groups, including free HA, and the association of HA and bilirubin had minimal impact.[278] Furthermore, the same study reported the role of HA nanoparticles conjugated to bilirubin in restoring intestinal barrier functions and reducing the level of apoptosis in the colonic epithelium. This formulation significantly reduced the local levels of proinflammatory cytokines, such as IL-1β, TNF-α, and IL-6, while increasing the levels of anti-inflammatory IL-10 and TGF-β cytokines.[278]

HA nanoparticles also modulate the gut microbiota, increasing the overall richness and diversity. HA nanoparticles covalently linked to bilirubin markedly increased the abundance of *Akkermansia muciniphila* (known to be associated with protective intestinal barrier functions[283]) and *Clostridium* XIVα, which are microorganisms with crucial roles in gut homeostasis.

5.3. Pectins

Pectins are a class of complex polysaccharides extracted from most terrestrial plants' cell walls, where they exert a function of controlling the movement of water and cementing for the cellulosic network.[284] They are known for their ability to form gels in the presence of calcium ions, solutes, or at low pH. Pectins are mainly composed of a linear chain of a homopolymer of α-(1,4)-D-galacturonic acid. The carboxylic acid groups on the backbone are methyl esterified at various degrees, thus controlling the gelling properties of pectins.[285] Pectins are a class of block copolymers because the linear chain termed ‘smooth region’ is occasionally interrupted by side chains composed of rhamnogalactomannan. This heteropolymer alternates (1,2)-α-L-rhamnosyl-(1-4)-α-D-galacturonic acid disaccharide units. These neutral chains tend to be gathered into particular areas of the pectin molecule are called ‘hairy regions’. There may be different branched blocks in pectins from one cell wall or even within a single pectin molecule. Notably, pectins with high hairy regions are less stable at low pH than pectins with smooth regions.

Pectins possess intrinsic anti-inflammatory activity depending on the degree of methylesterification.[286] Low methylesterification pectins would be a more efficient anti-inflammatory agent than high methylesterification pectins upon oral administration.[286] Low methylesterification pectin inhibited local and systemic inflammation, whereas high methylesterification pectins prevented intestinal inflammation.[286] When administered orally, pectins are subject to biodegradation by colonic bacteria. This property makes it ideal for targeted drug delivery to the colon.[287] In particular, pectins with low hairy regions and low methylesterification are more subject to degradation in the colon have been widely used to design colon-specific nanoparticulate DDS for the treatment of IBD. In addition to these advantages, pectins are known for their mucoadhesive properties,[288] making them ideal candidates to design colon-specific nanoparticulate DDS to alleviate IBD.

In a recent work conducted by Yener et al.,[289] pectin-based nanoparticles containing melatonin ameliorated the TNBS-induced IBD in rats by decreasing colonic fibrosis, oxidative stress, and inflammatory parameters of the colon. Melatonin was used as an antioxidant, anti-inflammatory, and radical scavenger drug. The nanoparticles formed by the polyelectrolyte complexation method using $CaCl_2$ had a mean hydrodynamic diameter of 75 nm and zeta potential of 24 mV. The same study revealed that pectin nanoparticles were 40 times more adherent to the inflamed rat's colon than the healthy colon mucosa, where the drug is released.[289]

The efficacy of pectin nanoparticles was further improved by adding HA in the formulation. The resulting hybrid particles (284 nm in size) were used to encapsulate Rhein as a natural anti-inflammatory ingredient.[290] According to physicochemical characterizations, the HA is located on the nanoparticles' outer shell that actively targets macrophages through CD44-mediated endocytosis. Biological evaluations revealed that the nanoparticles accumulated in the inflamed area of the colon of a DSS-induced UC mouse model. The nanoparticles protected the intestinal barrier of UC mice by acting on tight junction proteins.

5.4. Inulin

Inulin is a natural fructose polymer mainly derived from plants. Examples of plants that contain large quantities of inulin are Jerusalem artichoke, chicory root, asparagus root. It can also be found in consumed vegetables such as onion, banana, leek, garlic, rye, barley, and wheat. Inulin consists of linear chains of D-fructose units ($n = 2 - 60$) linked by β-(2,1)-glycosidic bonds and a terminal glucose residue (For review article on inulin structure and

physicochemical properties see reference[291]). Inulin containing a maximum 10 fructose units is also referred to as oligofructose. Inulin had several intrinsic biological properties, such as anti-inflammatory activity. It can promote the proliferation of beneficial intestinal bacteria (e.g., *Bifidobacterium and Lactobacillus*) and maintain intestinal micro-ecological balance and host health.[292, 293] In a pilot study, inulin-type fructans orally administered to patients with active UC induced functional but not compositional shifts of the gut microbiota. High dose administration of inulin-type fructans increased *Bifidobacteriaceae* and *Lachnospiraceae* abundance and increased SCFA levels.[294]

Inulin is a potential candidate for drug delivery to the colon because the presence of β-(2,1)-glycosidic bonds prevents its degradation in the upper part of the GI tract, while it gets degraded in the colon by colonic enzymes (e.g., ptyalin and amylase, which are adapted to digesting starch)[295] and bacteria (*Bifidobacteria*).[296]

Inulin has moderate solubility in water which decreases with temperature.[297] Inulin was hydrophobically modified by grafting carboxymethyl groups[298] hydrophobic dehydropeptide,[299] on hydroxyls present on inulin backbone to deliver hydrophobic drugs like glucocorticoids (e.g., budesonide) or nitroimidazole antibiotics (e.g., ornidazole)[300] for IBD treatment. In vivo results revealed that budesonide-loaded carboxymethyl inulin nanoparticles accumulate in inflamed colon tissue. Those systems showed enzyme- redox- and/or pH-sensitive properties allowing a specific drug release into the inflamed colon.[298, 299]

It has been reported that apremilast-loaded inulin nanoparticles can be coupled with mannose as a macrophage-targeting ligand.[197] Apremilast was used as a model anti-inflammatory drug for the treatment of IBD.[301] Mannosylated nanoparticles showed greater uptake in inflamed macrophages than the untreated macrophage and mannose receptor-negative cell lines. In vivo biodistribution exhibited 60% of mannosylated nanoparticles accumulated in the inflamed colon of UC mice. In addition to the colon-targeting property and anti-inflammatory activity of inulin, macrophage-targeted drug delivery could have promise for the treatment of IBD.[197]

Table 5: A list of significant polysaccharides used to monitor IBD.

Polysaccharides	**Origin**	**Role in IBD**
Chitosan	Exoskeleton of crustaceans[302, 303] The cell wall of	Different aspects of chitosan were explored for the monitoring of IBD: 1- As a carrier of conventional drugs due to its upper GI tract resistance properties[306]

	fungi[304, 305]	2- As a drug, where it can regulate different mechanisms: - Increasing the number of probiotics that regenerate the microbiota balance[307, 308] - Protecting the intestinal integrity by modulating the inflammation and oxidative stress[309] - Down-regulating the levels of macrophage-inflammatory protein (MIP)-2 in the serum. - Up-regulating the frequency of FoxP3+ T cells, which prevent the auto-immune attacks.
Hyaluronan (HA)	Various origins Traditionally: extraction from rooster combs Nowadays: streptococcal fermentation	HA is one of the glycosaminoglycans that is a significant component of the extracellular matrix of the intestinal mucosa,[310] where it has a crucial function of maintaining the translocation of luminal content into the general circulation. Although its mechanism of action is not yet fully understood, HA plays a significant role in immuno-inflammatory process due to its high affinity to the CD44 receptors that are overexpressed by the endothelial cells of the inflamed colonic segments. These receptors are crucial for infiltrating immune cells (e.g., monocytes, macrophages, neutrophils) in the inflamed tissues to aggravate the inflammation. Accordingly, the selective binding of HA to endothelial CD44 receptors during an inflammatory process will hamper the recruitment of immune cells.[311-313] In another study, Chen et al., explored the anti-inflammatory potential of high molecular HA (HM_W-HA) in reducing inflammation through a Toll-like receptor 4 (TLR4) modulation.[314] Indeed, TLR4 are widely distributed in the colon,[315] and they play a pivotal role in the colonic defense system. Their results confirmed their theory as HMw-HA reduced the TNBS induced colitis in wild-type mice but not in TLR4−/− mice.
Pectins	Various origins (e.g., orange, citrus, apple)	According to the origin of the extracted pectins, their role in IBD was reported to be different. Indeed, in one study, authors reported that pre-feeding mice with a side chain content of orange-extracted pectins had a protective effect of a TNBS-induced inflammation, whereas the pre-feeding with citrus-extracted pectins did not improve the clinical symptoms.[316] Pectins have a powerful impact on the downregulation of nuclear factor (NF)-κB p65 that is directly implicated in the immune response.[317]
Fructan	Angiosperms[318] (e.g., wheat, garlic, leeks, artichokes, agave)	Fructan, is reported to protect the intestinal mucosa due to its ability to enrich the mucosal intestine with probiotics. Indeed, Hino et al., suggested that a TNBS-induced colitis healing in rats could be a consequence of an increase in the number of lactic acid-producing bacteria following the ingestion of short-chain inulin-like fructan.[319] More recently, similar data were obtained at the clinical level, where inulin-type fructan showed

		clinical benefits in UC, as 77% of the patients showed a clinical response.[294]
Guar gum	Guar beans[251]	Guar gum participates in preventing and reducing UC by promoting the production of SCFAs. In a TNBS colitis model, it was demonstrated that partially hydrolyzed guar hum participated in the reduction of proinflammatory-cytokines, immune cells infiltration in the intestinal mucosa, and myeloperoxidase activity. Furthermore, another study reflected the wound healing of colonic epithelial cells and the repair of intestinal mucosa following the administration of partially hydrolyzed guar gum. The authors suggested that these observations would be a consequence of an up-regulation of extracellular signal-regulated kinases 1 and 2.

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7. Challenges and future directions

Nowadays, monitoring IBD relies on conventional drugs to prevent inflammation, alleviate the active phase, or modulate the immune response while using immunosuppressants. Nonetheless, using these drugs is often limited by either poor clinical efficiency or numerous side effects. Although the new biological therapies relying on the administration of monoclonal antibodies offer better management of the disease, their cost remains an obstacle for their ubiquitous use. Technological advances in designing nanoparticle-based therapies permitted the oral delivery of various drugs that would have found hurdles to reach the inflamed segment of the intestine after an oral administration. Nanoparticles exhibited many properties that make them suitable for the oral delivery of active drugs to alleviate IBD (e.g., ability to diffuse through mucus layer, mucoadhesive properties, passive targeting of the inflamed colon, and cell penetrability).

Polysaccharides, initially used for colon-specific drug delivery due to their biodegradability by bacterial enzymes, appear to be promising materials for designing nanoparticulate DDS for IBD treatment. The biocompatibility and the intrinsic activity of the polysaccharides, together with the advantages of the nanoparticulate systems, offer exceptional results in alleviating IBD. The most cited polysaccharides for IBD are chitosan and alginates. More recently, other polysaccharides were also investigated to alleviate IBD, such as hyaluronan, pectins, and inulin. Using those polysaccharides in combination (e.g., pectin and HA) is particularly interesting because it leads to multifunctional nanosystems with controlled properties such as drug release and receptor-mediated targeting. Furthermore, the synergism between the drug and the polysaccharide that have an intrinsic biological activity should be further explored in the future. Cui et al.,[126] recently reviewed this synergism between the drugs and polysaccharide-based carriers.

Overall, the results depicted from the numerous studies which investigated the use of polysaccharides as delivery systems are encouraging. Nonetheless, several hurdles need to be tackled. Most of the polysaccharides are both polymolecular and polydisperse. Their composition varies with the source and conditions of extraction, location, and other environmental factors. Thanks to fungi and bacteria fermentation processes, the sources of polysaccharides production have been diversified over recent years. Additional efforts should be made in this area to produce polysaccharides in reproducible and controlled manners.

A significant area of concern is to develop standardized methods for the in vitro evaluation of drug behaviors in simulated media of disease patients. Indeed, the simulated media usually used for in vitro investigations rather mimic healthy patients than patients suffering from IBD. IBD patients suffer from several physiological changes compared to healthy subjects. Those changes include pH in the GI tract, gut microbiota alteration, and variations in the colonic enzymes. This standardization should allow a better comparison between different research groups and a better correlation between in vitro and in vivo situations in humans. Furthermore, the models used to evaluate the mucoadhesion and the mucopenetration of nano-drug delivery were usually performed on mucus from healthy animals. In contrast, several changes in mucus, structure, composition, and viscoelastic properties were reported with the mucus of patients suffering from IBD. Alternative methods to evaluate the behaviors of nanoparticles toward mucus from animal models with induced inflammation should be developed.

Due to the complexity of IBD pathophysiology, the DSS and TNBS colitis models are far from mimicking the disease in humans. Passive targeting using eEPR was found to be weaker in humans compared to animal models. It has been increasingly clear that the intestinal microbiome is different in mice and humans. The pH in the mouse stomach varies from pH 2.7 to 4.1, while in humans, it can go down to pH 1.[320] However, the intestinal pH in mice was lower than in humans. Transit time, the mucus growth rate, and thickness are also different in mice and humans.[321] Mice mucus shows different levels of glycan profiles than humans. For a review article see reference [322]. Furthermore, only a few percent of the bacterial gene are shared between mice and humans.[322] Some receptors expressed by cells in mice are different from those in humans. Accurate animal models that mimic human IBD disease need to be developed in the future. Efforts were recently stressed on developing humanized mouse models,[323-325] or using large mammalian models such as pigs.[326]

Over the recent years, receptor-mediated targeting of immune cells showed promising preclinical results compared to non-targeted nanoparticulate DDS. However, the analysis of research articles in this field revealed that targeting strategies mainly focus on mannose receptor, CD44, and galactose agglutinin, while there are various receptors or cell adhesion molecules that are upregulated in the colon tissues of IBD.[327-330] Those receptors and cell adhesion molecules are still not applied to design targeted nanoparticles. Also, efforts should be devoted to understanding additional molecules implicated in the pathological process of IBD.

Another hurdle is related to the low encapsulation efficiency and the premature drug release of the encapsulated drug. Low encapsulation efficiency and premature drug release were tackled through the covalent linkage of the drug to the polysaccharide.[331-334] Compared with physical encapsulation, the prodrug strategy was explored for developing smart-responsive drug-polysaccharides conjugates.[331] In these systems, the drug was released under stimulus (e.g., pH, ROS, enzymes) for specific drug delivery at the site of inflammation.[298, 331, 335] However, the prodrug strategy could be limited by the availability of the appropriate functional groups of the drugs to be conjugated to the polysaccharide.

Finally, from a technological point of view, there are several well-known hurdles related to complex manufacturing processes of nanoparticles, the difficulty of scalability, and poor reproducibility.[336] These issues should be addressed by taking advantage of the considerable progress in the nanomedicine field these two last years. The psychological barrier to the clinical development of nanomedicines has been broken with the planetary commercialization of COVID vaccines composed of lipidic nanoparticles. The latest advances in lipid nanoparticles will undoubtedly orient future research works in the nanotechnology field. Today, we can rapidly overcome the technological and regulatory issues related to nanoparticle preparation and treatment processes after their preparations.

8. Conclusion

IBD remains one of the most challenging and less understandable diseases of the 21st century. Over the last couple of years, numerous medical and technological advances have allowed a better comprehension of the pathophysiology of IBD. Understanding immunological and proinflammatory signalling cascades has opened new avenues in monitoring the disease. Developing biological treatments relying on administrating monoclonal antibodies or siRNA targeting proinflammatory cytokines has gained much interest. Nonetheless, biologics are associated with some shortcomings, such as their expensive treatment or their reported loss of efficacy, partly because of the formation of anti-drug antibodies (ADAbs). Within these circumstances, new strategies are under investigation to develop new management protocols for IBD symptoms. Such strategies include nanotechnology or polysaccharide-based therapies. The principal target behind using engineered nanoparticles is to deliver a lower drug dosage to reach a higher therapeutic response. This strategy is possible because nanoparticles can target the API directly to the inflamed region of the colon, allowing to avoid the numerous systemic side effects of the

current medicines. Another characteristic of nanoparticles is their ability to protect fragile drugs from degradation in the harsh GI tract environments, allowing them to reach their site of action. More recently, polysaccharide-based therapies are gaining more interest as potential molecules for the monitoring of IBD. In fact, in addition to their high safety and low systemic side effects, polysaccharides were reported in numerous studies to play a prime role in regulating the inflammatory cytokines, the intestinal microbiome, and the immune system. These characteristics put polysaccharides on the spot of being an exciting alternative for currently available drugs.

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11. Abbreviations

5-ASA: 5-aminosalicylic acid

API: Active pharmaceutical ingredients

CD: Crohn disease

COX: Cyclooxygenase

CRF: Corticotrophin-releasing factor

CYA: Cyclosporine A

DA: Degree of acetylation

DDS: Drug delivery systems

eEPR: Epithelial enhanced permeability and retention

ES100: Eudragit S100

GALT: Gut-associated lymphoid tissue

GDNs: Grapefruit-derived nanovesicles

HA: Hyaluronan

HMw-HA: high molecular weight HA

IBD: Inflammatory bowel disease

Ig: Immunoglobulin

ILC: Innate lymphoid cells

KPV: Lysine-proline-valine

LMw-HA: low molecular weight HA

MAPK: Mitogen-activated protein kinase

MeO-PEG-b-PMOT: Methoxy-poly(ethylene glycol)-b-poly [4-(2,2,6,6-tetramethylpiperidine-1-oxyl)oxymethylstyrene]

NF-κB: nuclear factor-κB

NK: Natural killer

NLC: Nanostructured lipid carriers

NO: Nitroxide

PCL: Polycaprolactone

PEG: Poly(ethylene glycol)

PEI: Polyethyleneimine

PLGA/PLA-PEG-FA: Poly(lactic-*co*-glycolic acid)/poly(lactic acid)-polyethylene glycol-folic acid

ROS: Reactive oxygen species

SCFAs: Short-chain fatty acids

Silicon dioxide: SiO_2

TLR: Toll-like receptors

TNBS: Trinitrobenzosulfonic acid

TPP: Tripolyphosphate

UC: Ulcerative colitis