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Nanoparticle-enhanced mesalazine therapy for inflammatory bowel disease

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ABSTRACT

Inflammatory bowel disease (IBD) is a chronic inflammatory illness that causes ongoing bodily inflammation in the gastrointestinal tract. Drug-targeted delivery of aminosalicylates such as mesalazine at the inflammation sites, to treat ulcerative colitis (UC) and Crohn's disease (CD) has remained a difficulty. Current mesalazine formulations, including tablets, suppositories, and enemas, are typically associated with adverse systemic effects. The use of nanocarriers however has opened the possibility of improved local targeting and pharmacokinetics of loaded mesalazine, based on the new physicochemical properties of the drug vehicle. The innovative nanoencapsulation of mesalazine has demonstrated success in targeting inflammatory regions and treating mild to moderate IBD. The use of nanocarriers, such as lipid-based, polymeric, and inorganic nanocarriers, has demonstrated improved overall solubility, absorption, and bioavailability of mesalazine while minimising the side effects associated with their absorption. This review aims to offer an insight into what is currently known about IBD, and the nanotechnological approaches for the improvement of mesalazine therapy for IBD.

1. Introduction

Inflammatory bowel disease (IBD) is a worldwide health concern with a steadily rising prevalence. It is distinguished by persistent chronic inflammation in the intestine. It is a collective term for two serious illnesses: ulcerative colitis (UC) and Crohn's disease (CD) [1]. IBD's acute signs include constipation, abdominal discomfort, bloody stools, and fatigue. Colorectal cancer is a chronic symptom of IBD that typically appears after certain years of untreated IBD [2]. The European Federation of Crohn's & Ulcerative Colitis Associations (EFCCA) estimates that 10 million people globally suffer from IBD [3]. Besides, an analysis performed in 2022 by Crohn's & Colitis UK indicated that 1 in every 123 individuals in the UK has either UC or CD [3]. Moreover, a current study on IBD discovered that people with IBD have a marginally lower life expectancy than people without the condition [3]. In contrast to the general population, 7% of IBD patients with extensive colonic involvement over time appear to be at substantially increased risk of colorectal cancer [4–7].

2. Immunological pathogenesis of IBD

The cause of IBD is unclear. However, inflammation in the body is believed to be caused by a weakened immune system [8]. Furthermore, the commensal microbes in the digestive tract are a contributing component in the induction of inflammation. The gut microbiota plays an important part in regulating gut health. In healthy individuals, the intestinal microbiota has a symbiotic relationship with their host. They carry out several critical and unique functions, including metabolic functions, and maintaining the mucous barrier by preventing the breach of pathogens, along with enhancing epithelial layer integrity, and immune-modulatory effects [9]. Numerous potential factors, including genetic (problems with autophagy, antimicrobial peptides, bacterial management, and cytokines) and environmental (smoking, anxiety, infections, excessive use of antibiotics, lack of vitamin D, and diet affecting the microclimate of the gastrointestinal epithelial cells), play a significant role in the initiation of intestinal inflammation and impair the body's immunological tolerance mechanism, due to the imbalance of gut microbiota and commensal bacteria becoming pathogenic [10]. Human commensal microbiota (Clostridium and Bifidobacterium) predominates less frequently in IBD sufferers, while unfavourable bacteria (*E. coli* and organisms that break down sulphate) are more prevalent. Subsequently, the pathogenesis of IBD is characterised by bacterial death, dysbiosis leading to a deficient innate immune system, and an overly aggressive adaptive immune reaction [8].

IBD also has a genetic component, so if either parent has the disease, the child is more likely to develop it. Several interleukins (IL)-23 pathway sub-units, including IL23R, IL12B, signal transducer and activator of transcription 3 (STAT3), Janus kinase 2 (JAK2), and tyrosine kinase 2 (TYK2), are IBD susceptibility genes that are known to be linked

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Abbreviations

IBD	Inflammatory bowel disease
UC	Ulcerative colitis
CD	Crohn's disease
TNF-alpha	Tumour necrosis factor-alpha
AhR	Aryl hydrocarbon receptor
SLNs	Solid lipid nanoparticles
NLCs	Nanostructured lipid carriers
TNBS	2,4,6-Trinitrobenzene sulfonic acid
SLMs	Solid lipid microparticles
PAMAM	Poly(amidoamine)
PGE-2	Prostaglandin E2
HPMCP	Hydroxypropyl methylcellulose phthalate
DSS	Dextran sulphate sodium
COX-2	Cyclooxygenase-2
iNOS	Inducible nitric oxide synthase
MPO	Myeloperoxidase
PLGA	Poly(lactic-co-glycolic acid)
ACG	Acetylated cashew gum
MAP	Modified apple polysaccharides
DAI	Disease activity index
Nrf2	Nuclear factor erythroid 2-related factor 2

to UC and CD formation [11]. As illustrated in Fig. 1 Microfold/M cells, directed by genetic and environmental factors, gather antigens from the lumen and actively transport them to the underlying lymphoid follicles (aggregation of immune cells). Eventually, the immune cells in the intestine initiate the activation process, causing the intestine barrier function to deteriorate. Antigens are processed by the antigen-presenting cells/macrophages activate T cells to stimulate the production of cytokines such as tumour necrosis factor-alpha (TNF-α), IL-1, and IL-16. This results in continuous inflammation in the intestines. The inflammation can cause problems with digesting food and absorbing nutrients, water, and electrolytes, leading to malnutrition. The current cohort analysis of adult patients with newly diagnosed IBD (disease duration of $\leq$18 months) found that 36% fulfilled malnutrition criteria and 8% had $\geq$1 micronutrient deficiency [12].

The inflammatory cells responsible for CD and UC are identical. It is believed to be primarily mediated by T helper 1 (Th1) and T helper 2 (Th2) cells, and more recently, T helper 17 (Th17) cells [13]. Recent research suggests that Th17 cells are the primary cause of inflammation in IBD. Th17 cells generate pro-inflammatory cytokines, which usually cause tissue damage and play a pathological role in the progression of autoimmune disease [14]. They are distinguished by the production of interleukin 17 (IL-17), as well as several inflammatory mediators [15]. The generation of Th17 cells typically occurs when T cells are activated by the presence of cytokines (IL-6 and TGF-β).

UC is typically defined by a proclivity for ulcers in the lumen or interior lining of the large intestine, which encompasses both the proximal colon and the rectum. The ileocecal region of the digestive system suffers the most from this condition [16]. Colitis is a risk factor for colorectal cancer, which most commonly manifests in the rectal sigmoid area. This malignancy is caused by bowel perforation or rupture. UC can cause fistulas, abscesses, stenosis, tenesmus, rectal urgency, and abnormal lymphoid growth [17]. There are various types of UC based on the region of the colon that is inflamed: Ulcerative proctitis, which is restricted to the rectum, is the milder version of UC that is more manageable; pancolitis, which causes inflammation throughout the colon; distal colitis, which affects the left side of the colon [18]. Contrarily, CD is a chronic inflammatory disease that can affect any part of the digestive system. Abdominal pain, fever, and diarrhoea with blood and mucus are some of the early signs of CD [17] (Fig. 2).

3. Current treatments for IBD and their challenges

The range of IBD treatment choices has grown over the last few years. Since the past, if lifestyle measures do not work, aminosalicylates (mesalazine or sulfasalazine), corticosteroids (prednisolone, methylprednisolone, budesonide, or intravenous hydrocortisone) and immunosuppressants (azathioprine, mercaptopurine, ciclosporin or methotrexate) were used to induce and maintain remission. Antibiotics (metronidazole, ciprofloxacin) may be needed, alongside biological drugs such as tumour necrosis factor-alpha (TNF-alpha) inhibitors (infliximab, adalimumab, ustekinumab or vedolizumab), Janus kinase inhibitors, and sphingosine-1-phosphate receptor modulators, to improve treatment and alleviate symptoms. However, these drugs, based on their individual mechanisms of action, are associated with a substantial risk of systemic side effects in IBD patients [19]. In addition, another challenge with IBD treatment is that IBD is chronic with no curative treatment, therefore long-term medication is required. Besides, IBD is often not controlled by monotherapy alone, with add-on treatment necessary, such as corticosteroids added to aminosalicylates, leading to a build-up of side effects. Depending on the severity, surgical resection may also be required.

Currently, mesalazine, also known as mesalamine or 5-amino salicylic acid, is the first-line treatment for IBD treatment. It is the active ingredient of the pro-drug sulfasalazine (mesalazine connected to sulphapyridine as the carrier through diazo bonding, Fig. 3), which has been used to manage IBD for over 80 years [16]. Mesalazine exerts its action by interfering with the metabolism of arachidonic acid, which involves prostaglandin and leukotriene conversion, reactive oxygen species gathering, and cytokines production [20]. Mesalazine was discovered to activate regulatory T cells (Tregs) in the colon via the aryl hydrocarbon receptor (AhR) pathway, followed by TGF-β activation [21,22]. Tregs suppress the immune response, thereby maintaining homeostasis and self-tolerance, and TGF-β regulates inflammation in the gut. Mesalazine has success rates of 40%–70% and remission rates of 15%–20% in mild and chronic IBD [23]. According to Murray et al. (2020), a once-daily dosing of oral mesalazine has comparable benefits to a standard (twice or three times daily) dosing and is more potent than a placebo in treating UC [24]. Moreover, according to a case-control study, maintenance therapy with mesalazine can lower UC patients' risk of colorectal cancer by 75% [25]. For sustaining surgically induced remission of CD in individuals with mild to moderate CD, mesalazine treatment was found to be better than a placebo, and safe in comparison to anti-TNF-α [26]. Flatulence, nausea, abdominal discomfort, diarrhoea, and headache are some of the milder side effects, and therefore may be preferred because they have fewer side-effects than other treatments. However, it was also reported that within a year of receiving mesalazine, a small number of individuals could experience nephrotoxicity [21,27]. The systemic side effects associated with mesalazine have led scientists to investigate nanocarriers for targeted delivery to improve the drug's local bioavailability.

Inflammatory-targeted drug delivery is being explored via the use of nanocarriers containing mesalazine, for the selective and local accumulation of the drug vehicles at the sites of inflammation in the digestive tract, increasing the therapeutic efficacy there. These drug vehicles are colloidal particles with submicron sizes that are typically less than 500 nm [28]. Because of the site-specific delivery of the drug, the nanocarriers are beneficial in terms of improved pharmacokinetics and local biodistribution, lower systemic toxicity, increased solubility, and absorption, and potentially an adjustable controlled release profile [28–30]. Mesalazine has already been shown to reduce inflammation

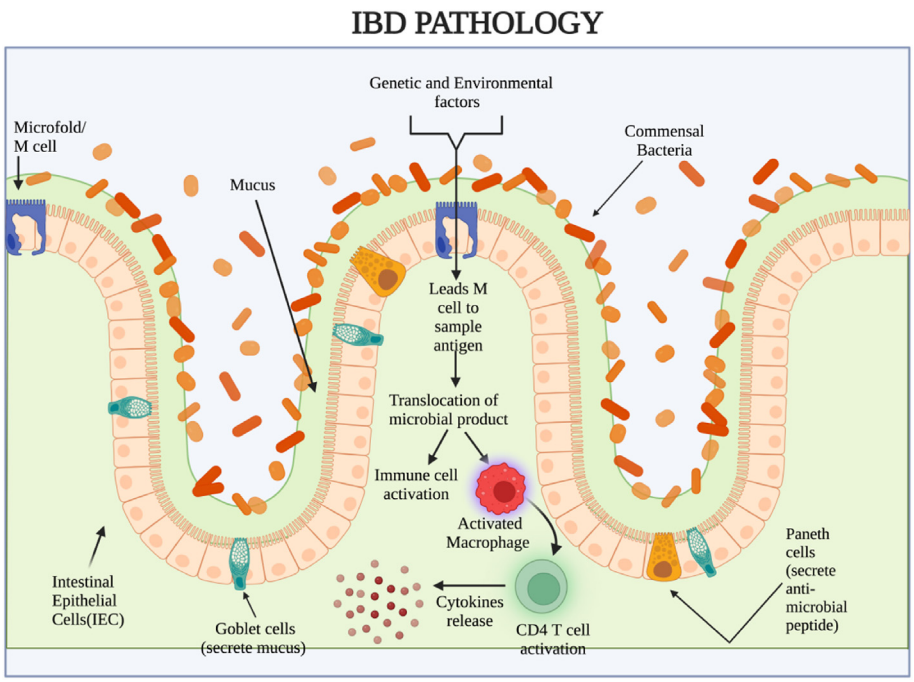

Fig. 1. Illustration of the pathogenesis of IBD. Microfold/M cells, directed by genetic and environmental factors, gather antigens from the lumen and actively transport them to the underlying lymphoid follicles (aggregation of immune cells). Antigens processed by the antigen-presenting cells/macrophages activate T cells to stimulate the production of cytokines such as tumour necrosis factor-alpha (TNF-α), IL-1, and IL-16. This results in continuous inflammation in the intestines. Image created with Biorender .com.

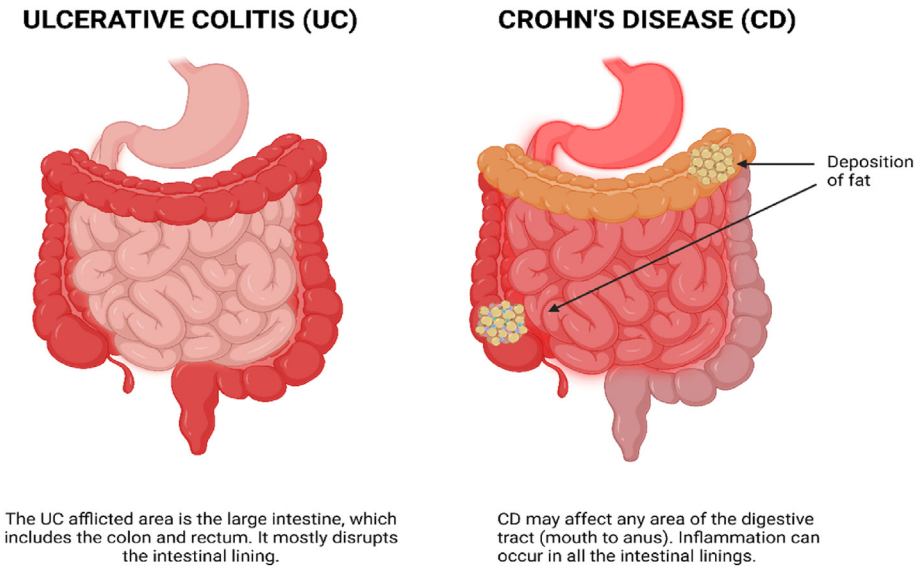

Fig. 2. The distinction between UC and CD is illustrated by the fact that UC affects the small intestine, whereas CD affects the digestive tract as well as the small intestine. Image created by Biorender.com.

locally on the colonic mucosa using rectal foam, suppositories, and enemas. Further encapsulating mesalazine in nanocarriers is anticipated to prolong its colonic residency time and enhance its accumulation in inflamed tissues. Moreover, controlled release of mesalazine into inflamed bodily compartments through nano-encapsulation will allow for a reduction in dose, thereby reducing the side effects associated with absorption.

4. Novel nanocarriers for IBD treatment

Several investigations have discovered that the small size of the nanocarriers (less than 500 nm) preferentially targets the inflammatory colonic region [21]. The colonic residence duration may also be extended by reducing the size of the nanocarriers, leading to selective accumulation within the inflammatory tissues. During the state of intense inflammation, more nanocarriers are taken up by immune-reactive cells, which reduces inflammation by reducing cytokines synthesis [28,31,32]. Moreover, due to the high ratio of surface area to volume of nanocarriers, this can modify the physicochemical properties of the drug (mesalazine is a BCS Class IV drug – low permeability and low solubility). This is also dependent on the choice of the drug's carrier, whether it is hydrophilic or hydrophobic. The three main classes of nanocarriers are described below (Table 1).

4.1. Lipid-based nanocarriers

Lipid-based nanocarriers are spherical vesicles composed of ionizable lipids that are neutral at physiological pH. They can release their payload into the cells via endocytosis, depending on their size. Furthermore, the behaviour of lipid nanocarrier is influenced by lipid type, size, and surface charge [33] (see Fig. 4).

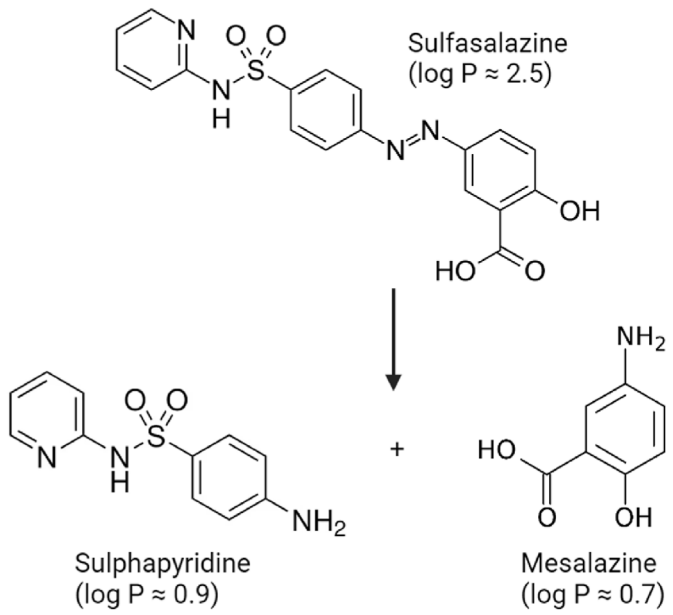

Fig. 3. Mesalazine is the active ingredient of the pro-drug sulfasalazine, which is connected to sulphapyridine as the carrier through diazo bonding.

4.1.1. Liposomes

Liposomes are colloidal spherical structures produced by the self-assembly of amphiphilic lipid molecules like phospholipids [34]. They are made up of one or two phospholipid bilayers that are arranged around the aqueous layer, with a hydrophobic tail and a hydrophilic head. This structure enables liposomes to have a higher drug-loading capability [35,36]. Liposomes are regarded as a type of effective drug delivery vehicle due to their small particle size, biocompatibility, biodegradability, non-toxicity, and non-immunogenicity. Liposomes can mimic natural cell membranes at the cellular level, allowing for excellent interaction between liposomes and mammalian cell membranes and encouraging efficient cellular uptake, which increases penetration [37].

Orally ingested formulations lead to systemic absorption, but liposomal formulations have allowed for local treatment within the gastrointestinal tract. In an *in-vivo* study, a pH-sensitive liposomal formulation (coated with Eudragit S100) for mesalazine and curcumin (a natural compound that reduces the development of chronic experimental colitis and alleviates the inflammatory response) was administered orally in guinea pigs to treat UC [38]. The uncoated liposomes were less stable and degraded in the stomach, where most of the drug was lost (83% of the mesalazine and 82% of the curcumin were released at pH 1.2) and only a trace reached the intestines [38]. The coated ones, on the other hand, showed pH-sensitive release, with a minimal quantity of each drug lost at pH 1.2 and maximum release at pH 7.4, demonstrating the greatest level of therapeutic effectiveness [38]. Another *in-vivo* study examined the anti-inflammatory effects of mesalazine and chlorogenic acid (plant--derived anti-inflammatory compound) encapsulated in liposomes on mice. The effect of liposomal mesalazine and chlorogenic acid was assessed macroscopically along with measuring myeloperoxidase activity. When compared to chlorogenic acid, liposome-encapsulated mesalazine proved effective in treating colitis by decreasing macroscopic scores (such as ulcer score, faecal blood) and microscopic scores (such as goblet cell depletion, degree of immune cell infiltration) [39].

4.1.2. Solid lipid nanoparticles (SLNs)

Due to their hydrophobic core, SLNs are frequently used as durable nanocarriers for drugs with poor solubility. The minimal toxicity, extended drug release, efficient cellular absorption, and large surface area of SLNs are their most noteworthy characteristics [40,41]. The drug release from SLNs is determined by the matrix type and drug position in the formulation. SLNs made of biodegradable and biocompatible components can combine both hydrophilic and lipophilic bio-actives, useful for combination therapies, making them a feasible choice for controlled and targeted drug delivery [41,42].

Mesalazine loaded within SLNs was characterized in an *in-vivo* study to ascertain the surface properties, colon targetability, and drug release. According to the findings, SLNs had an encapsulation efficiency of 56–72 %. After 24 h, rat caecal media (the first portion of large bowel) revealed an 87.3% mesalazine release from alginate-coated SLNs. Additionally, a 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis model was used to assess the therapeutic capability of SLNs. Mesalazine loaded in SLNs demonstrated significantly less histological damage, inflammatory cell infiltration, and colon tissue weight/length ratios as compared to free mesalazine. The final findings demonstrated that the alginate coating assisted in hindering the mesalazine release in the upper gastrointestinal tract [43]. Another study investigated the effect of different lipids on the encapsulation, solubility, and extended release of mesalazine using solid lipid microparticles (SLMs) produced from various lipid options. Cetyl palmitate was found to be more effective at solubilising mesalazine and preventing mesalazine ejection from lipid matrices. Furthermore, the thermal study demonstrated the high chemical stability of SLMs and they maintain the effective encapsulation of the mesalazine [40,44].

4.1.3. Nanostructured lipid carriers (NLCs)

NLCs are second-generation lipid nanoparticles that also focus on enhancing drug loading. NLCs are binary systems that contain both solid and liquid lipids, resulting in a less organized lipidic core. This internal design facilitates more drug accommodation than SLNs [45]. They outperform other common lipid-based nanocarriers such as SLNs in terms of stability, low toxicity, increased shelf life, drug loading capacity, and biocompatibility [46].

In one study, mesalazine and curcumin were loaded into NLCs through high-pressure homogenization. The drug release results revealed that NLCs improved mesalazine release at 48 h by 100% and curcumin release at 120 h by 82.23 ± 2.97% [47]. Furthermore, there was a considerable drop in nitric oxide levels during the formulation's anti-inflammatory evaluation on RAW264.7 cells, indicating that the formulation has a high potential to treat inflammation. This formulation necessitates an investigation of animal models to establish its anti-inflammatory potential in living beings [47].

4.2. Polymeric nanocarriers

Polymeric nanocarriers are drug delivery vehicles ranging in size from 1 to 1000 nm that can be loaded with drugs that are either entrapped within the polymeric core or are surface-adsorbed. Polymer-based nanocarriers offer a diverse set of drug encapsulation efficiencies, targeting moieties, and stimuli-responsive properties, allowing them to be employed in a wide range of drug administration strategies, useful for IBD patients [48,49] (see Fig. 5).

4.2.1. Dendrimer

Dendrimers are synthetic, polyfunctionalised, poly-branched, tree-like polymers with precise size, shape, and chemical functionality that can deliver drugs to specific locations [50].

In an *in-vitro* investigation, the creation of a new nanocarrier system based on poly (amidoamine) (PAMAM) dendrimer of the fourth generation was employed to produce larger concentrations of mesalazine in intestinal epithelial cells, hence boosting its anti-inflammatory potential [51]. The biophysical assessment of this formulation revealed that the PAMAM-mesalazine conjugate considerably increased the hydrodynamic diameter of the nanoparticles, therefore they diffuse slower compared to free mesalazine in the dialysis experiment [51]. The break-up or hydrolysis of PAMAM-mesalazine is the rate-limiting step, but it did not alter with pH within the normal range of 7.4 (cytoplasmic) to 5 (lysosomal). PAMAM is demonstrated to have the capacity to deliver high

Table 1
List of mesalazine-loaded nanocarriers for IBD treatment.

No.	Nanocarriers	Composition	Method of preparation	Main findings	Reference
1.	Liposomes	Non-hydrogenated soybean phosphatidylcholine, Eudragit S-100, stearyl amine, and cholesterol.	Thin-film hydration	The pH-sensitive release of curcumin-mesalazine-loaded liposomes coated with Eudragit S100 was 83%.	[38]
2.	Solid lipid nanoparticles	Solid lipids, emulsifier, sodium alginate (0.4% w/v), and solvent	Not applicable	In the TNBS-induced colitis model, mesalazine-loaded SLNs caused less histological damage, inflammatory cell infiltration, and colon tissue weight/length ratios than free mesalazine.	[43]
3.	Nanostructured lipid carrier (NLCs)	Solid lipids such as glyceryl monostearate (GMS), palmitic acid (PA), stearic acid (SA), span 40 (S-40) and span 60 (S-60). Liquid lipids such as Labrafil 1944 M CS (LMCS), Capmul MCM (CMCM), Labrafac PG (LPG), olive oil, peanut oil cinnamon oil, and castor oil. Surfactant and co-surfactants such as diethylene monoethyl ether, Tween 80 (T-80), Tween 20 (T-20), polyethylene glycol 200 (PEG 200), and Span-20.	High-pressure homogenization followed by probe sonication	NLCs increased mesalazine release by 100% after 48 h. There was also a decrease in nitric oxide levels in cells, showing the ability to cure inflammation.	[47]
4.	Dendrimer	Central core, branches, and exterior surface with functional groups.	Not applicable	Mesalazine-loaded dendrimers lowered marker gene expression and duplicated the anti-inflammatory effect on cells.	[51]
5.	Chitosan nanoparticles	Hydroxypropyl-β-cyclodextrin, chitosan, sodium TPP.	Freeze-drying method	Mesalazine-loaded chitosan NPs released 70% of the drug. They reduced nitric oxide, PGE-2, and IL-8 production.	[53]
		Acetic acid, HPMCP (hydroxypropyl methylcellulose phthalate), Trehalose dihydrate, hydrochloric acid, sodium hydroxide, 3-(4, 5-dimethylthiazol-2-yl)-2, 5 diphenyl tetrazolium bromide (MTT), pepsin from porcine gastric mucosa (P7000), and pancreatin from porcine pancreas (P3292), and chitosan.	Ionic gelation	At low doses, chitosan NPs and mesalazine both boosted survival. They improved the ulcer index and DAI increased colon length, and decreased colon wet weight.	[54]
6.	Gelatin nanoparticles	Gelatin, Eudragit-S100, surfactant.	Nanoprecipitation	Mesalazine-loaded gelatin NPs raise levels of myeloperoxidase, inducible nitric oxide synthase, and inflammatory biomarkers.	[57]
7.	PLGA nanoparticles	PLGA, ethanol, dichloromethane (DCM), and surfactants.	Single oil-in-water (o/w) emulsion/solvent evaporation method	Positively charged nanoparticles may significantly increase nanoparticle entrapment through the epithelium layer of intestinal tissue.	[59]
		PLGA, alginic acid sodium salt, dichloromethane (DCM), latex beads, and dyes.	Double emulsion method	PLGA NPs demonstrated zero organoid development, demonstrating their biocompatibility and lack of toxicity.	[60]
8.	Zein nanoparticles	Zein, lysine, mannitol, ethanol, and purified water.	Desolvation method with subsequent spray drying	Mesalazine demonstrated persistent release from zein NPs (97.67 ± 0.32%) over 120 h. They had good biocompatibility and the potential to transfer mesalazine to the colon.	[63]
9.	Cashew gum nanoparticles	Acetyled cashew gum, acetone, and ultra-pure water.	Dialysis method and solvent displacement	ACG NPs showed improved colon absorption and no basal cytotoxicity in CT26 cells up to 131 μg/mL.	[65]
10.	Core-shell nanoparticles	Dimethyl sulfoxide, aqueous solution, chitosan, alginate, Eudragit®S100, Tetrabutylammonium Hydrogen Sulphate, fluorescent marker.	Anti-solvent crystallization technology	Eudragit®S100 coated core-shell NPs demonstrated 15.85% mesalazine at pH 1.2 and 6.8 and were able to release mesalazine slowly and sustainably at pH 7.4, demonstrating that they can prevent oral drug release in the upper GIT and transfer the drug to the colon more efficiently.	[68]
11.	Silica nanoparticles	Silica, cyclohexane, butanol, polyoxymethylene nonylphenol ether, tetraethyl orthosilicate, acetonitrile, and distilled water. Not applicable	Micro-emulsion method Drug-SiNP coupling	Cytotoxicity of silica has reduced the survival rates of Caco-2 cells. In another *in-vivo* investigation, Me5-ASA-loaded SiNPs exhibited preferential attachment to inflammatory tissues, establishing a reservoir at the inflamed region over healthy surrounding tissues in mice.	[71] [72]
12.	Silver nanoparticles	Malus domestica, silver nitrate, sodium nitrate, Ethanol, sulphuric acid, copper acetate, aerosil (A-200), hydroxy furfural acetate, disodium hydrogen phosphate, potassium dihydrogen phosphate and trehalose.	Not applicable	Mesalazine-loaded AgNPs exhibited 54% at the colonic site, providing greater therapeutic efficacy for the treatment of UC compared to free mesalazine.	[74]
13.	Zinc oxide nanoparticles	Not applicable	Not applicable	Mesalazine-loaded ZnO NPs reduced the expression of pro-inflammatory cytokines such as TNF- and IL-1 in the DSS-treated colon.	[80]

intracellular loads of mesalazine, as PAMAM-mesalazine managed to concentration-dependently suppress the expression of marker genes, with higher level of inhibition in comparison to free mesalazine. It is anticipated to produce the same effect *in vivo* [51].

4.2.2. Chitosan nanoparticles

Chitosan offers a wide range of pharmaceutical and biomedical applications due to its worldwide availability, biocompatibility, biodegradability, high drug loading capacity, and non-toxicity. Chitosan's slow biodegradation allows for the regulated and prolonged release of loaded

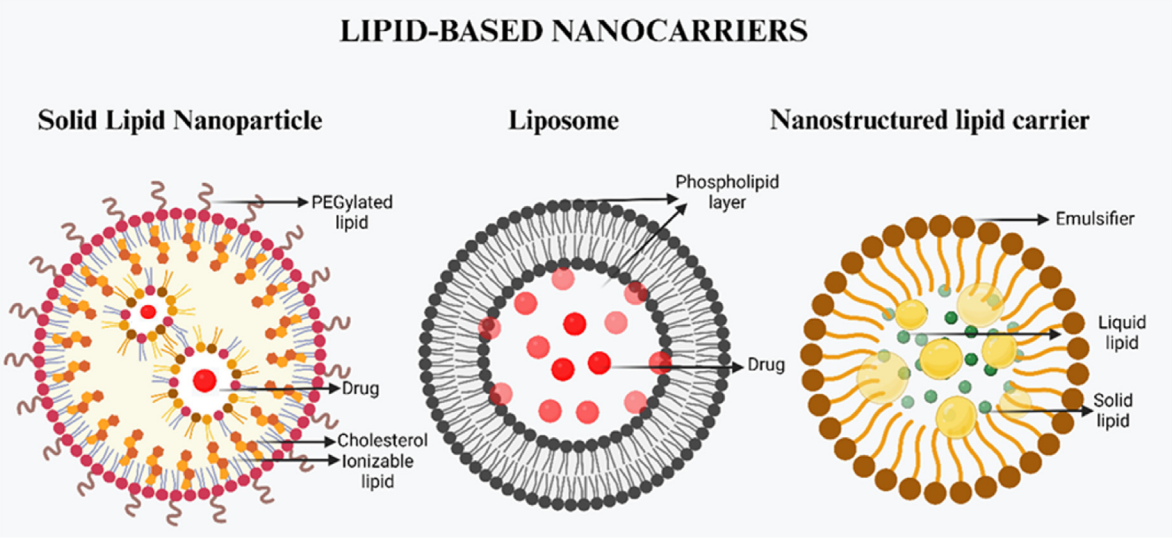

Fig. 4. Illustration of IBD lipid nanocarriers. Solid-lipid nanoparticles, liposomes, and nanostructured lipid carriers are lipid-based nanocarriers that aid in enhancing solubility, bioavailability, permeability, and cellular penetration while reducing the side effects associated with the drug's absorption. Image created with Biorender.com.

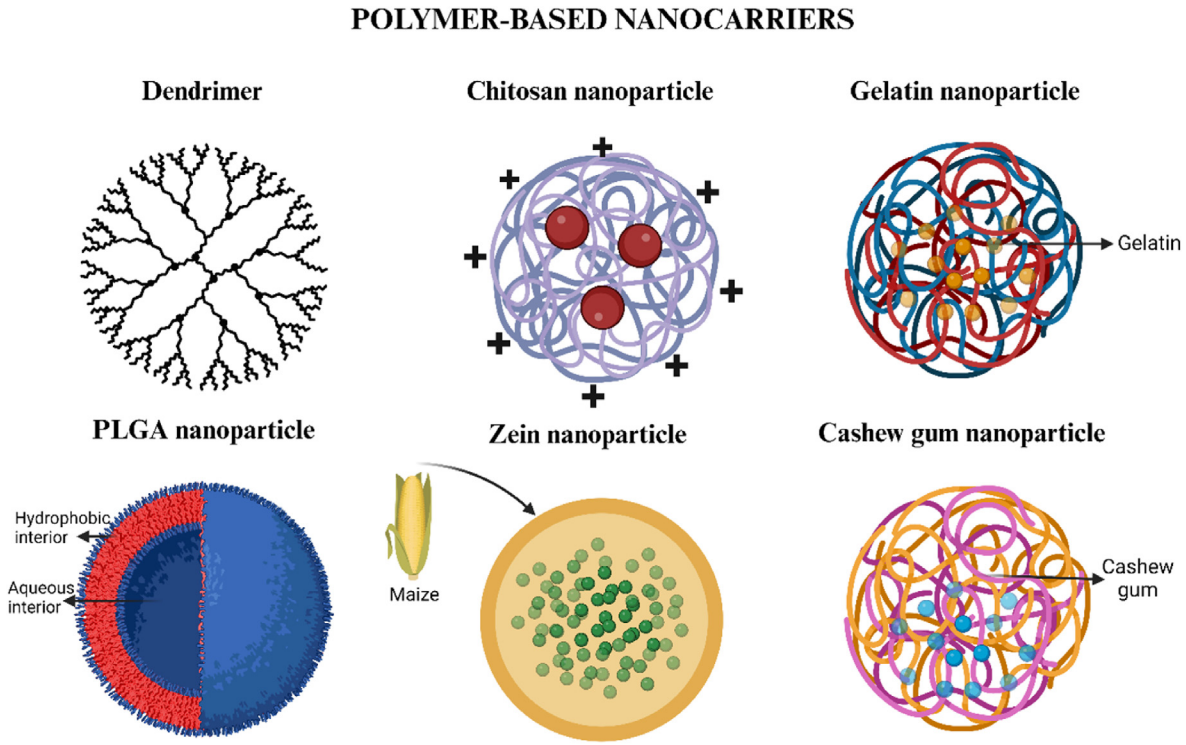

Fig. 5. Polymer-based nanocarriers for IBD are depicted. The polymeric nanocarriers depicted above have a distinct structure that aids in decreasing cytotoxicity, preventing premature drug release, and boosting drug stability and bioavailability. They have a broad mix of drug encapsulation efficiencies, targeting moieties, and stimuli-responsive features that enable them to be used in a variety of drug delivery techniques. Image created with Biorender.com.

molecules, which lowers the need for frequent dosage, and aids in increasing patient compliance with IBD treatment [52]. In the administration of anti-inflammatory drugs, where rapid clearance of the active moiety due to increased tissue permeability is the main issue, chitosan offers mucoadhesion, making it an appealing choice. Active drug moieties can be passively targeted to inflammatory areas due to the pH-dependent drug release characteristics of chitosan, through the inclusion of a deacetylated primary amine group in its chemical structure [33]. Chitosan has a low p*K*a value ranging from 6.2 to 7.0. The polymer's amine groups undergo protonation under acidic circumstances, resulting in the positively charged chitosan interacting with the gastrointestinal mucosa for prolonged residency duration at the site.

In an *in-vitro* study, the rectal formulation of mesalazine was produced by synthesising a hydroxypropyl-cyclodextrin inclusion complex loaded with chitosan nanoparticles [53]. In cytokine-stimulated HT-29 cell lines, the activity of this rectal formulation against a cytokine-triggered inflammatory response was assessed by monitoring major inflammatory mediators [53]. When compared to the free drug, the drug loaded in the chitosan nanoparticles (release percentage of 70% after 24 h, which was significantly higher than the 20% of free

mesalazine) suppressed the generation of nitric oxide, prostaglandin E2 (PGE-2), and IL-8, indicating that the chitosan nanoparticles together with mesalazine may have stronger anti-inflammatory effects for IBD treatment [53]. Another *in-vivo* study used hydroxypropyl methylcellulose phthalate (HPMCP) as a cross-linker in the preparation of mesalazine and berberine (an alkaloid) in chitosan nanoparticles to inhibit early drug release in the upper gastrointestinal tract of rats [54]. In 8 h, 45.04 % of mesalazine and 82.32% of berberine were released at pH 7.2 [54]. Contrarily, no significant drug release was seen at pH 1.2, indicating that drug release was hindered in the stomach, and that mesalazine's release rate steadily increased as it moved from the stomach to the colon [54]. Similarly, the chitosan-bound ginger extract (*Zingiber officinale*) nanocarrier loaded with mesalazine was evaluated *in-vitro* [55]. The nanocarrier's water sorption capacity and a slow and regulated release of the mesalazine from the chitosan-bound ginger nanocarrier at pH 6.8 was found to be ideal for IBD treatment [55].

4.2.3. Gelatin-based nanoparticles

Gelatin is a biocompatible, hydrophilic, and biodegradable polymer formed by partial hydrolysis of collagen that has been widely used as a drug delivery medium [56].

Gelatin-based nanoparticles were reported to facilitate the oral delivery of mesalazine to a dextran sulphate sodium (DSS)-induced UC mouse model by targeting colon tissues, where they displayed colitis-protective properties [57]. The Eudragit-S100-coated and mesalazine-loaded gelatin nanoparticles managed to bypass abrasive gastric surroundings, subsequently gain access to colonic mucosa, accumulate at the inflammatory cells to regulate levels of inflammatory biomarkers (TNF-α, IL-1, cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and myeloperoxidase (MPO)) [57].

4.2.4. Poly (lactic-co-glycolic acid) (PLGA)

PLGA is a biodegradable, biocompatible, and hydrophobic polyester. Because of its use clinically, for its breakdown properties, and prolonged drug delivery potential, PLGA is the one of the most widely used polymers in pharmaceutics [58].

The effect of surface charge on the delivery of mesalazine-loaded PLGA nanoparticles into the lumen of organoids was investigated in an *ex-vivo* study. Alginate (negatively charged) and chitosan (positively charged) were utilised as nanoparticle-coating agents. The use of either alginate or chitosan-coated nanoparticles had no effect on organoid growth or viability. Moreover, it showed that the positive charge of the chitosan-coated PLGA nanoparticles had allowed them to be transported across the epithelial layer into the lumen than the alginate-coated nanoparticles [59]. The reason behind the positively charged nanoparticles can penetrate cell membranes more deeply is hypothesised to be due to their interactions with the anionic glycoproteins of the epithelial cells. Charge neutralisation enables differential opening of the tight junctions to occur. Chitosan's mucoadhesive characteristics allow them to adhere to mucosal membranes and gradually release the loaded drug [59]. In another study, PLGA nanoparticles were loaded with mesalazine and a dye, Rhodamine B, showing most of the NPs depositing in the intestinal lumen [60]. The normal growth of organoids in nanoparticle-containing samples compared to the control sample suggested that PLGA NPs have no effect on organoid growth, showing biocompatibility, and non-toxicity [60].

4.2.5. Zein nanoparticles

Zein, a flexible polymer, serves as the main protein in maize. Zein is mucoadhesive and resistant to gastrointestinal surroundings. It is an amphiphilic prolamin with well-defined hydrophobic and hydrophilic domains that can self-assemble into nanoparticles. These nanoparticles have demonstrated their use in drug encapsulation and delivery applications, especially as a potential vehicle for the cellular uptake, bioavailability, and controlled release of drugs [61,62].

Mesalazine was encapsulated in zein nanoparticles through

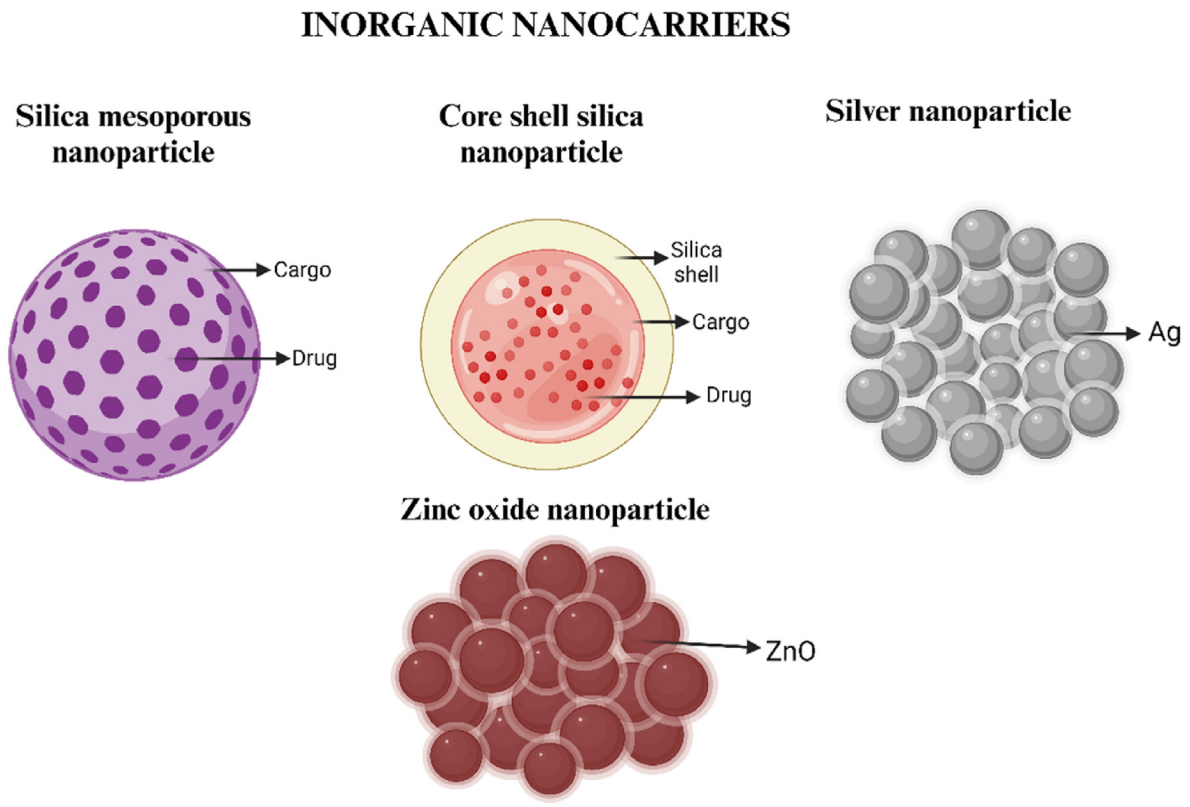

Fig. 6. Illustration of inorganic nanocarriers for IBD. Inorganic nanocarriers have been shown to aid in boosting cellular absorption and diffusion of nanoparticles. They have also been shown to reduce disease activity index, antioxidant levels, and tumour necrosis factors. Image created with Biorender.com.

desolvation for oral delivery to the colon, with an encapsulation efficiency of 45% [63]. The *in-vitro* release tests showed gastrointestinal tolerance and a sustained drug release at pH 7.4 (97.67 ± 0.32%) over the course of 120 h. When the nanoparticles were tested for cytotoxicity on the CT26 (murine colon adenoma) cell line, they did not exhibit any cytotoxicity up to a concentration of 500 μg/mL, demonstrating good biocompatibility [63].

4.2.6. Acetylated cashew gum (ACG) nanoparticles

Cashew gum, a naturally occurring polysaccharide obtained from the exudate of the *Anacardium occidentale* tree, can be used in nanostructured systems to achieve more controlled release and gastrointestinal protection by having its molecular structure improved through acetylation [64].

A study has demonstrated the improvement of mesalazine absorption in the colon after being encased in ACG nanoparticles [65]. Crystalline mesalazine was made more stable by being incorporated into ACG nanoparticles. According to the *in-vitro* release experiments, raising the pH to 6.8 increased the drug release to 62.08 ± 6.03%. This level of release persisted at pH 7.4 where a sustained release of 95.61 ± 3.25% was observed. Moreover, ACG nanoparticles (with or without mesalazine) showed no basal cytotoxicity in CT26 cells up to a dose of 131 μg/mL, demonstrating ACG nanoparticles as promising mesalazine delivery vehicles [65].

4.2.7. Core-shell nanoparticles

Core-shell nanoparticles have a distinct structure that includes an inner core and an outer shell, which could be made of different polymers. Core-shell nanoparticles have sparked extensive interest due to their improved stability, lower cytotoxicity, and improved biocompatibility [66]. Their primary functions are to prevent the premature release of drugs from nanoparticles, enhancing drug absorption and minimising adverse effects [67,68].

In recent work, mesalazine was loaded into core-shell nanoparticles generated by layer-by-layer self-assembly of nanocrystals coated with chitosan, Eudragit S100, and sodium alginate. The encapsulation efficiency was determined to be 95.05 ± 3.83% [68]. Only 15.85% mesalazine was released at both pH 1.2 and 6.8, with further slow and sustained release at pH 7.4, showing that they can prevent oral drug release in the upper gastrointestinal and transport the drug to the colon more efficiently [68]. The *in-vivo* analysis of core-shell nanoparticles confirmed the selective accumulation in the mice's colon. Furthermore, the mucous-penetrating experiment demonstrated that the multilayer polymer structure considerably improved the mucous penetration capacity of the core-shell nanoparticles, enhancing their therapeutic impact on the treatment of UC [68].

4.3. Inorganic nanocarriers

Inorganic nanocarriers are metal or metal oxide-derived nanocarriers. The most commonly researched inorganic nanocarriers for IBD are silica, silver, and zinc oxide nanoparticles (see Fig. 6).

4.3.1. Silica/Silicon dioxide (SiO_2) nanoparticles

Silica nanoparticles typically range from 10 to 500 nm in size and have various shapes and physicochemical properties. While size and shape are the main factors in the uptake and biodistribution of nanoparticles, the delivery of the payload is also strongly influenced by porosity. Silica nanoparticles can be mesoporous or non-porous. The porosity of silica nanoparticles can be adjusted between 2 and 50 nm by varying the synthesis conditions. Mesoporous silica nanoparticles have the benefits of adjustable uniform pore size, large surface area, and pore volumes [69,70].

Mesalazine-loaded silica nanoparticles were used to examine the nanocarrier's therapeutic efficacy on the inflamed region of the UC mouse model. Although the cytotoxicity of silica has reduced the survival rates of Caco-2 cells, in the current investigation, silica nanoparticles containing 100 mg/kg of mesalazine showed similar efficacy to mesalazine solution at a dose of 400 mg/kg [71]. In another study, silica nanoparticles were loaded with methyl-5-ASA (Me5-ASA) as a drug delivery vehicle for selective accumulation in inflamed colonic tissues on 2, 4,6-trinitrobenzene sulfonic acid (TNBS) induced colitis model of mice [72]. In the drug release experiment, Me5-ASA and mesalazine were discovered in the release medium, with a relatively increasing amount of mesalazine with time [72]. Me5-ASA-loaded silica nanoparticles also showed preferential attachment to inflammatory tissues, forming a reservoir at the inflamed site, in comparison to the mice's healthy surrounding tissues [72].

4.3.2. Silver (Ag) nanoparticles

Silver nanoparticles, with a size between 1 and 100 nm, due to their distinctive metallic characteristics, surface-to-volume ratio, and capacity to produce a variety of nanostructures, have been explored as a nanocarrier for drug delivery for IBD [73].

One recent study has used silver nanoparticles capped with modified apple polysaccharide (MAP) loaded with mesalazine to treat UC in a rat model [74]. The encapsulation efficiency in silver nanoparticles was very high (93 ± 3.21%) [74]. After 5 h, the dissolution analysis demonstrated 54% mesalazine release at the colonic site, which offers superior therapeutic efficacy for the treatment of UC in comparison to free mesalazine or silver nanoparticles alone [74]. In the *in-vitro* cell line toxicity assessment, mesalazine in silver nanoparticles were shown to have more than 86% of the cells viable at a dose of 4 μg/mL. Furthermore, an *in-vivo* investigation showed that this formulation reduced the disease activity index (DAI), antioxidant levels, and tumour necrosis factor after the seventh and fourteenth days of colitis induction [74].

4.3.3. Zinc oxide (ZnO) nanoparticles

Zinc oxide nanoparticles play a vital role in demonstrating anti-inflammatory properties, making them a promising candidate for treating IBD [75]. Their intrinsic anti-inflammatory properties include mechanisms such as inhibiting inducible nitric oxide synthase (iNOS) enzyme expression [76], inhibiting pro-inflammatory cytokine release [77], inhibiting myeloperoxidase [78], and inhibiting the NF- pathway [79].

Mesalazine-loaded zinc oxide nanoparticles were used in one study to treat mice with DSS-induced colitis [80]. The oral treatment of empty zinc oxide and zinc oxide loaded with mesalazine in mice revealed a decrease in myeloperoxidase (MPO) activity [80]. The data also showed that the zinc oxide nanoparticles decreased the expression of pro-inflammatory cytokines such as TNF-α and IL-1β in the DSS-treated colon [80]. Additionally, by triggering the nuclear factor erythroid 2-related factor 2 (Nrf2) signalling pathway, the nanoparticles provided protection against colitis brought on by DSS. The effects of the zinc oxide nanoparticles on the disease's remission were dose-dependent [80]. It was therefore concluded that this combo therapy worked well for mice treated with DSS-induced colitis.

5. Discussion

Existing mesalazine products on the market, such as Octasa, Pentasa, Zintasa, Mezavant, and Salofalk, contain mesalazine in its free drug form. Alarming side effects to watch out for include unexplained bleeding, bruising, red or purple discolorations of the skin, an unexplained sore throat or high temperature, diarrhoea, abdominal pain, nausea, and muscle aches, which affect one in every ten people [81].

Inflammation-targeted drug delivery would be an attempt to reduce the occurrence of these side effects. Formulating mesalazine using nanocarriers, as described in this review, whether it be passive (small particle size, particle composition) or active targeting (pH, surface charge), have shown to increase accumulation in the inflamed region of the digestive tract in animal models, thereby enhancing local

bioavailability. In particular, electrostatic interaction has allowed for these nanocarriers to target inflamed colonic epithelium. Positively charged lipids improve binding to the site of inflammation [82], similar to positively charged polymeric nanoparticles such as chitosan, by specifically interacting with the negatively charged mucosal surface of the inflamed colon [83]. These nanocarriers with high drug loading capacity also provide increased apparent solubility and sustained and regulated the release of the drug. The coating of lipid-based and polymeric nanocarriers, as demonstrated in this review, plays an important role in preventing drug release in the upper gastrointestinal tract and reducing chances for absorption into the systemic circulation. Moreover, unlike polymeric or lipid nanocarriers, metallic nanocarriers exhibit high interstitial fluid pressure stability. They can be more easily transported across inflamed cells for the treatment of IBD.

Despite the aim for inflammation-targeted drug delivery, nanoparticles with small particle size may still enter the blood circulatory system through unintended routes following administration. They are capable of penetrating cell membranes, entering organelles, and upsetting cell physiology, which can result in cytotoxicity and genotoxicity [84]. Apart from the particle size, the absorption of nanoparticles by cells as well as how they interact with organelles and biomolecules may also be influenced by the shape and surface charge [85]. Typically, the toxicity of nanoparticles increases as the surface charge increases, which is required for the prevention of agglomeration of the nanoparticles. Although there have been some promising toxicity studies on cell viability in the literature above, more stringent and standardized testing methodologies are required before the clinical translation of mesalazine-containing nanocarriers. The colloidal nano-formulations of mesalazine for *in-vitro* and *in-vivo* experimentations will also need to be re-formulated for human use, therefore, re-characterisations may be necessary. Details of further *in-vivo* safety profiling of the excipients utilised in nanocarriers will pave the way for the development of safe and effective nano-enhanced mesalazine therapy for IBD in human [86].

6. Conclusion and perspective

This review paper summarises the most current applications of mesalazine-loaded nanocarriers for the treatment of IBD. IBD is a long-standing chronic condition that causes ongoing inflammation in the gastrointestinal tract. Mesalazine has shown high success rate of inducing and maintaining remission of IBD, however, comes with some alarming systemic side effects. The article focuses on nanocarriers formulated with mesalazine, such as lipid-based nanocarriers, polymer-based nanocarriers, and inorganic nanocarriers, which have been shown to target the inflamed regions of the gastrointestinal tract, provide controlled release of the drug while also minimise adverse effects associated with mesalazine absorption. The nanocarriers can overcome inflamed colonic barriers, which include a thick mucus layer, disturbed epithelium, and altered colonic transit time. In particular, mucoadhesive, enteric-coated, and positively charged nanocarriers were found to be the most effective in targeting the inflamed areas. Once the safety profile of these nanocarriers is fully established, and with such an array of nanocarriers described and discussed in this paper, it is anticipated that nano-enhanced mesalazine therapy for IBD will be highly beneficial for IBD patients.

Availability of data and material

Not applicable.

Author contributions

Rajvanshi Sutaria: performed literature research, analysis, and drafted the paper. Zi Hong Mok: supervised the work, provided insights, revised, and improved the paper. All authors have read and agreed to the published version of the manuscript.

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Not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Y.Z. Zhang, Y.Y. Li, Inflammatory bowel disease: pathogenesis, World J. Gastroenterol.: WJG 20 (1) (2014 Jan 1) 91. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3886036/.
[2] What Is Inflammatory Bowel Disease (IBD)?, Centers for Disease Control and Prevention, 2022. Available at: https://www.cdc.gov/ibd/what-is-IBD.htm.
[3] S. Khalid, IBD Statistics 2022: Crohn's and Ulcerative Colitis, Ampersand Health, 2022 May 12. Available at: https://ampersandhealth.co.uk/myibdcare/resources/ibd-statistics-2022-crohns-and-ulcerative-colitis/.
[4] T. Jess, C. Rungoe, L. Peyrin–Biroulet, Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies, Clin. Gastroenterol. Hepatol. 10 (6) (2012 Jun 1) 639–645. Available at: https://www.sciencedirect.com/science/article/abs/pii/S1542356512001097.
[5] M.W. Lutgens, F.P. Vleggaar, M.E. Schipper, P.C. Stokkers, C.J. van der Woude, D.W. Hommes, D.J. de Jong, G. Dijkstra, A.A. van Bodegraven, B. Oldenburg, M. Samsom, High frequency of early colorectal cancer in inflammatory bowel disease, Gut 57 (9) (2008 Sep 1) 1246–1251. Available at: https://pubmed.ncbi.nlm.nih.gov/18337322/.
[6] J.A. Eaden, K.R. Abrams, J.F. Mayberry, The risk of colorectal cancer in ulcerative colitis: a meta-analysis, Gut 48 (4) (2001 Apr 1) 526–535. Available at: https://gut.bmj.com/content/48/4/526.short.
[7] C.P. Selinger, J.M. Andrews, A. Titman, I. Norton, D.B. Jones, C. McDonald, G. Barr, W. Selby, R.W. Leong, Sydney IBD Cohort Study Group, Long-term follow-up reveals low incidence of colorectal cancer, but frequent need for resection, among Australian patients with inflammatory bowel disease, Clin. Gastroenterol. Hepatol. 12 (4) (2014 Apr 1) 644–650. Available at: https://pubmed.ncbi.nlm.nih.gov/23707778/.
[8] Q. Guan, A comprehensive review and update on the pathogenesis of inflammatory bowel disease, Journal of immunology research (2019 Oct), 2019. Available at: https://www.hindawi.com/journals/jir/2019/7247238/.
[9] F. Fava, S. Danese, Intestinal microbiota in inflammatory bowel disease: friend of foe? World J. Gastroenterol.: WJG 17 (5) (2011 Feb 2) 557. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3040327/.
[10] G.P. Ramos, K.A. Papadakis, Mechanisms of disease: inflammatory bowel diseases, InMayo Clinic Proceedings 94 (1) (2019 Jan 1) 155–165. Elsevier. Available at: https://www.sciencedirect.com/science/article/abs/pii/S0025619618307511.
[11] S.C. Park, Y.T. Jeen, Genetic studies of inflammatory bowel disease-focusing on Asian patients, Cells 8 (5) (2019 May 1) 404. Available at: https://www.mdpi.com/2073-4409/8/5/404.
[12] S.L. Gold, L.G. Rabinowitz, L. Manning, L. Keefer, W. Rivera-Carrero, S. Stanley, A. Sherman, A. Castillo, S. Tse, A. Hyne, K. Matos, High prevalence of malnutrition and micronutrient deficiencies in patients with inflammatory bowel disease early in disease course, Inflamm. Bowel Dis. 29 (3) (2023 Mar) 423–429. Available at: https://academic.oup.com/ibdjournal/article-abstract/29/3/423/6589577.
[13] Z.J. Liu, P.K. Yadav, J.L. Su, J.S. Wang, K.E. Fei, Potential role of Th17 cells in the pathogenesis of inflammatory bowel disease, World J. Gastroenterol.: WJG 15 (46) (2009 Dec 12) 5784. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2791270/.
[14] M.B. Torchinsky, J.M. Blander, T helper 17 cells: discovery, function, and physiological trigger, Cell. Mol. Life Sci. 67 (2010 May) 1407–1421. Available at: https://link.springer.com/article/10.1007/s00018-009-0248-3.
[15] K.E. Marks, S. Flaherty, K.M. Patterson, M. Stratton, G.J. Martinez, J.M. Reynolds, Toll-like receptor 2 induces pathogenicity in Th17 cells and reveals a role for IPCEF in regulating Th17 cell migration, Cell Rep. 35 (13) (2021 Jun 29) 109303. Available at: https://www.sciencedirect.com/science/article/pii/S2211124721006793.
[16] M. Gajendran, P. Loganathan, G. Jimenez, A.P. Catinella, N. Ng, C. Umapathy, N. Ziade, J.G. Hashash, A comprehensive review and update on ulcerative colitis, Disease-a-Month 65 (12) (2019 Dec 1) 100851. Available at: https://www.sciencedirect.com/science/article/pii/S0011502919300318.

[17] D.C. Baumgart, W.J. Sandborn, Crohn's disease, Lancet 380 (9853) (2012 Nov 3) 1590–1605. Available at: https://www.sciencedirect.com/science/article/pii/S0140673612600269.
[18] Ulcerative Colitis, Mayo Clinic, Mayo Foundation for Medical Education and Research (MFMER), 2022. Available at: https://www.mayoclinic.org/diseases-conditions/ulcerative-colitis/symptoms-causes/syc-20353326.
[19] S.S. Seyedian, F. Nokhostin, M.D. Malamir, A review of the diagnosis, prevention, and treatment methods of inflammatory bowel disease, Journal of medicine and life 12 (2) (2019 Apr) 113. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6685307/.
[20] N.A. Punchard, S.M. Greenfield, R.P. Thompson, Mechanism of action of 5-arninosalicylic acid, Mediat. Inflamm. 1 (3) (1992 Jan 1) 151–165. Available at: https://www.hindawi.com/journals/mi/1992/480976/.
[21] Z. Cai, S. Wang, J. Li, Treatment of inflammatory bowel disease: a comprehensive review, Front. Med. 8 (2021 Dec 20) 765474. Available at: https://www.frontiersin.org/articles/10.3389/fmed.2021.765474/full.
[22] K. Oh-Oka, Y. Kojima, K. Uchida, K. Yoda, K. Ishimaru, S. Nakajima, J. Hemmi, H. Kano, Y. Fujii-Kuriyama, R. Katoh, H. Ito, Induction of colonic regulatory T cells by mesalamine by activating the aryl hydrocarbon receptor, Cellular and molecular gastroenterology and hepatology 4 (1) (2017 Jul 1) 135–151. Available at: https://www.sciencedirect.com/science/article/pii/S2352345X1730073.
[23] R. Karagozian, R. Burakoff, The role of mesalamine in the treatment of ulcerative colitis, Therapeut. Clin. Risk Manag. 3 (5) (2007 Oct 30) 893–903. Available at: https://www.tandfonline.com/doi/full/10.2147/tcrm.s12160468.
[24] A. Murray, T.M. Nguyen, C.E. Parker, B.G. Feagan, J.K. MacDonald, Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis, Cochrane Database Syst. Rev. (8) (2020). Available at: https://pubmed.ncbi.nlm.nih.gov/32786164/.
[25] J. Eaden, K. Abrams, A. Ekbom, E. Jackson, J. Mayberry, Colorectal cancer prevention in ulcerative colitis: a case-control study, Alimentary pharmacology & therapeutics 14 (2) (2000 Feb 1) 145–153. Available at: https://europepmc.org/article/med/10651654.
[26] M. Gordon, K. Naidoo, A.G. Thomas, A.K. Akobeng, Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease, Cochrane Database Syst. Rev. (1) (2011). Available at: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008414.pub3/references.
[27] J.P. Gisbert, Y. González-Lama, J. Maté, 5-Aminosalicylates and renal function in inflammatory bowel disease: a systematic review, Inflamm. Bowel Dis. 13 (5) (2007 May 1) 629–638. Available at: https://pubmed.ncbi.nlm.nih.gov/17243140/.
[28] F. ud Din, W. Aman, I. Ullah, O.S. Qureshi, O. Mustapha, S. Shafique, A. Zeb, Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors, Int. J. Nanomed. 12 (2017) 7291. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634382/.
[29] C.W. How, A. Rasedee, S. Manickam, R. Rosli, Tamoxifen-loaded nanostructured lipid carrier as a drug delivery system: characterization, stability assessment and cytotoxicity, Colloids Surf. B Biointerfaces 112 (2013) 393–399, https://doi.org/10.1016/j.colsurfb.2013.08.009.
[30] B.B.T.S. Mishra, B.B. Patel, S. Tiwari, Colloidal nanocarriers: a review on formulation technology, types and applications toward targeted drug delivery, Nanomed. Nanotechnol. Biol. Med. 6 (1) (2010) 9–24, https://doi.org/10.1016/j.nano.2009.04.008.
[31] V. Thakur, B. Singh, A. Sharma, N. Kumari, I. Kumar, K. Verma, A. Kumar, S. Rana, Importance of nanocarriers and probiotics in the treatment of ulcerative colitis, Int. J. Appl. Pharm. 13 (1) (2021) 77–85. Available at: https://pdfs.semanticscholar.org/f35a/a51906cdaced2ae56c15ebb36e304ce64f40.pdf.
[32] A.L. Lamprecht, N. Ubrich, H. Yamamoto, U. Schäfer, H. Takeuchi, P. Maincent, Y. Kawashima, C.M. Lehr, Biodegradable nanoparticles for targeted drug delivery in treatment of inflammatory bowel disease, J. Pharmacol. Exp. Therapeut. 299 (2) (2001 Nov 1) 775–781. Available at: https://pubmed.ncbi.nlm.nih.gov/11602694/.
[33] Let's Talk about Lipid Nanoparticles, Nature Publishing Group, 2021. Available at: https://www.nature.com/articles/s41578-021-00281-4.
[34] C. Sebaaly, H. Greige-Gerges, S. Stainmesse, H. Fessi, C. Charcosset, Effect of composition, hydrogenation of phospholipids and lyophilization on the characteristics of eugenol-loaded liposomes prepared by ethanol injection method, Food Biosci. 15 (2016 Sep 1), 1-0. Available at: https://www.infona.pl/resource/bwmeta1.element.elsevier-ac9418fc-8a52-36d8-9dc6-afe9254e4bf7.
[35] R. Nisini, N. Poerio, S. Mariotti, F. De Santis, M. Fraziano, The multirole of liposomes in therapy and prevention of infectious diseases, Front. Immunol. 9 (2018 Feb 5) 155. Available at: https://www.frontiersin.org/articles/10.3389/fimmu.2018.00155/full.
[36] D. Guimarães, A. Cavaco-Paulo, E. Nogueira, Design of liposomes as drug delivery system for therapeutic applications, Int. J. Pharm. 601 (2021 May 15) 120571. Available at: https://pubmed.ncbi.nlm.nih.gov/33812967/.
[37] L. Sercombe, T. Veerati, F. Moheimani, S.Y. Wu, A.K. Sood, S. Hua, Advances and challenges of liposome assisted drug delivery, Front. Pharmacol. 6 (2015 Dec 1) 286. Available at: https://www.frontiersin.org/articles/10.3389/fphar.2015.00286/full.
[38] S. Aib, K. Iqbal, N. Khan, S. Khalid, M. Adnan, S.M. Umair, M.J. Dar, pH-sensitive liposomes for colonic co-delivery of mesalazine and curcumin for the treatment of ulcerative colitis, J. Drug Deliv. Sci. Technol. 72 (2022 Jun 1) 103335. Available at: https://www.sciencedirect.com/science/article/pii/S0144861723003521.
[39] J.B. Krajewska, P. Pietruszka, D. Tomczyk, C. Chen, A. Owczarek, B. Karolewicz, H. Czapor-Irzabek, A. Gorniak, J. Fichna, Evaluation of the effect of liposomes loaded with chlorogenic acid in treatment of 2, 4, 6-trinitrobenzenesulfonic acid-induced murine colitis, J. Physiol. Pharmacol. 70 (2019 Apr 1) 269–275. Available at: https://pubmed.ncbi.nlm.nih.gov/31443089/.
[40] C. Jori, A.A. Chaudhary, S. Rashid, M.A. Ali, A.S. Alawam, F. Haouala, R. Khan, Biomaterial-based strategies for immunomodulation in IBD: current and future scenarios, J. Mater. Chem. B (2023). Available at: https://pubs.rsc.org/en/content/articlehtml/2023/tb/d3tb00276d.
[41] V. Mishra, K.K. Bansal, A. Verma, N. Yadav, S. Thakur, K. Sudhakar, J.M. Rosenholm, Solid lipid nanoparticles: emerging colloidal nano drug delivery systems, Pharmaceutics 10 (4) (2018 Oct 18) 191. Available at: https://www.mdpi.com/1999-4923/10/4/191.
[42] K.H. Ramteke, S.A. Joshi, S.N. Dhole, Solid lipid nanoparticle: a review, IOSR J. Pharm. 2 (6) (2012 Nov) 34–44.
[43] M. Wang, W. Hao, L. Zhang, Y. Zhu, K. Chen, S. Ma, X. Cheng, J. Zhao, Lipid-polymer nano core-shell type hybrid system for colon specific drug delivery, J. Drug Deliv. Sci. Technol. 63 (2021 Jun 1) 102540. Available at: https://www.sciencedirect.com/science/article/abs/pii/S1773224721002203.
[44] E.F. Silveira, L. Rannier, L. Nalone, C.F. da Silva, M.V. Chaud, M. de, R. Barbosa, R.L. Junior, L.P. da Costa, E.B. Souto, P. Severino, Loading of 5-aminosalicylic in solid lipid microparticles (SLM) solubility screening of lipid excipients and physicochemical characterization, J. Therm. Anal. Calorim. 139 (2020 Jan) 1151–1159. Available at: https://link.springer.com/article/10.1007/s10973-019-08544-7.
[45] M. Elmowafy, M.M. Al-Sanea, Nanostructured lipid carriers (NLCs) as drug delivery platform: advances in formulation and delivery strategies, Saudi Pharmaceut. J. 29 (9) (2021 Sep 1) 999–1012. Available at: https://www.sciencedirect.com/science/article/pii/S1319016421001420.
[46] J. Garg, K. Pathania, S.P. Sah, S.V. Pawar, Nanostructured lipid carriers: a promising drug carrier for targeting brain tumours, Future Journal of Pharmaceutical Sciences 8 (1) (2022 Apr 8) 25. Available at: https://link.springer.com/article/10.1186/s43094-022-00414-8.
[47] A. Awasthi, B. Kumar, M. Gulati, S. Vishwas, L. Corrie, J. Kaur, R. Khursheed, R.A. Muhammed, D. Kala, O. Porwal, M.R. Babu, Novel nanostructured lipid carriers co-loaded with mesalamine and curcumin: formulation, optimization and in vitro evaluation, Pharmaceut. Res. 39 (11) (2022 Nov) 2817–2829. Available at: https://link.springer.com/article/10.1007/s11095-022-03401-z.
[48] V. Lenders, X. Koutsoumpou, A. Sargsian, B.B. Manshian, Biomedical nanomaterials for immunological applications: ongoing research and clinical trials, Nanoscale Adv. 2 (11) (2020) 5046–5089. Available at: https://pubs.rsc.org/en/content/articlelanding/2020/na/d0na00478b.
[49] A. Zielińska, F. Carreiró, A.M. Oliveira, A. Neves, B. Pires, D.N. Venkatesh, A. Durazzo, M. Lucarini, P. Eder, A.M. Silva, A. Santini, Polymeric nanoparticles: production, characterization, toxicology and ecotoxicology, Molecules 25 (16) (2020 Aug 15) 3731. Available at: https://www.mdpi.com/1420-3049/25/16/3731.
[50] A. Singh, G. Singh, U.K. Mandal, R.K. Narang, Smart nanocarriers: a novel tool for the treatment of ulcerative colitis, Pharma 12 (2020 Apr) 37–43. Available at: https://www.isfcppharmaspire.com/article_html.php?did=13829&issueno=0.
[51] M. Gorzkiewicz, M. Marcinkowska, M. Studzian, I. Karwaciak, L. Pulaski, B. Klajnert-Maculewicz, Mesalazine–PAMAM nanoparticles for transporter-independent intracellular drug delivery: cellular uptake and anti-inflammatory activity, Int. J. Nanomed. (2023 Dec 31) 2109–2126. Available at: https://www.tandfonline.com/doi/full/10.2147/IJN.S390763.
[52] P. Rajitha, D. Gopinath, R. Biswas, M. Sabitha, R. Jayakumar, Chitosan nanoparticles in drug therapy of infectious and inflammatory diseases, Expet Opin. Drug Deliv. 13 (8) (2016 Aug 2) 1177–1194. Available at: https://pubmed.ncbi.nlm.nih.gov/27087148/.
[53] P. Tang, Q. Sun, L. Zhao, H. Pu, H. Yang, S. Zhang, R. Gan, N. Gan, H. Li, Mesalazine/hydroxypropyl-β-cyclodextrin/chitosan nanoparticles with sustained release and enhanced anti-inflammation activity, Carbohydr. Polym. 198 (2018 Oct 15) 418–425. Available at: https://europepmc.org/article/med/30093018.
[54] S. Mahami, M. Salehi, M. Mehrabi, H. Vahedi, M.S. Hassani, F.S. Bitaraf, A. Omri, pH-sensitive HPMCP-chitosan nanoparticles containing 5-aminosalicylic acid and berberine for oral colon delivery in a rat model of ulcerative colitis, Int. J. Biol. Macromol. (2023 Jun 10) 125332. Available at: https://www.sciencedirect.com/science/article/pii/S0141813023022262.
[55] R. Markam, A.K. Bajpai, Functionalization of Ginger Derived Nanoparticles with Chitosan to Design Drug Delivery System for Controlled Release of 5-amino Salicylic Acid (5-ASA) in Treatment of Inflammatory Bowel Diseases: an in Vitro Study. Reactive and Functional Polymers, vol. 149, 2020 Apr 1 104520. Available at: https://www.sciencedirect.com/science/article/pii/S1381514819308120.
[56] D.F. Li, M.F. Yang, H.M. Xu, M.Z. Zhu, Y. Zhang, C.M. Tian, Y.Q. Nie, J.Y. Wang, Y.J. Liang, J. Yao, L.S. Wang, Nanoparticles for oral delivery: targeted therapy for inflammatory bowel disease, J. Mater. Chem. B 10 (31) (2022) 5853–5872. Available at: https://pubs.rsc.org/en/content/articlehtml/2022/tb/d2tb01190e.
[57] A. Ahmad, M.M. Ansari, R.K. Mishra, A. Kumar, A. Vyawahare, R.K. Verma, S.S. Raza, R. Khan, Enteric-coated gelatin nanoparticles mediated oral delivery of 5-aminosalicylic acid alleviates severity of DSS-induced ulcerative colitis, Mater. Sci. Eng. C 119 (2021 Feb 1) 111582. Available at: https://www.sciencedirect.com/science/article/pii/S0928493120335001.
[58] H.K. Makadia, S.J. Siegel, Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier, Polymers 3 (3) (2011 Aug 26) 1377–1397. Available at: https://www.mdpi.com/2073-4360/3/3/1377.
[59] Z. Davoudi, N. Peroutka-Bigus, B. Bellaire, A. Jergens, M. Wannemuehler, Q. Wang, Gut organoid as a new platform to study alginate and chitosan mediated PLGA nanoparticles for drug delivery, Mar. Drugs 19 (5) (2021 May 20) 282. Available at: https://www.mdpi.com/1660-3397/19/5/282.

[60] Z. Davoudi, N. Peroutka-Bigus, B. Bellaire, M. Wannemuehler, T.A. Barrett, B. Narasimhan, Q. Wang, Intestinal organoids containing poly (lactic-co-glycolic acid) nanoparticles for the treatment of inflammatory bowel diseases, J. Biomed. Mater. Res. 106 (4) (2018 Apr) 876–886. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/jbm.a.36305.

[61] S. Tortorella, M. Maturi, V.V. Buratti, G. Vozzolo, E. Locatelli, L. Sambri, M.C. Franchini, Zein as a versatile biopolymer: different shapes for different biomedical applications, RSC Adv. 11 (62) (2021) 39004–39026. Available at: https://pubs.rsc.org/en/content/articlehtml/2021/ra/d1ra07424e.

[62] D. Wang, S. Tao, S.W. Yin, Y. Sun, Y. Li, Facile preparation of zein nanoparticles with tunable surface hydrophobicity and excellent colloidal stability, Colloids Surf. A Physicochem. Eng. Asp. 591 (2020 Apr 20) 124554. Available at: https://www.sciencedirect.com/science/article/pii/S0927775720301473.

[63] I.B. Lima, L.C. Moreno, A.V. Peres, A.C. Santana, A. Carvalho, M.H. Chaves, L. Lima, R.W. Sousa, D. Dittz, H.M. Rolim, L.C. Nunes, Nanoparticles obtained from zein for encapsulation of mesalazine, Pharmaceutics 14 (12) (2022 Dec 16) 2830. Available at: https://www.mdpi.com/1999-4923/14/12/2830.

[64] A.J. Ribeiro, F.R. de Souza, J.M. Bezerra, C. Oliveira, D. Nadvorny, M.F. Soares, L.C. Nunes, E.C. Silva-Filho, F. Veiga, J.L. Sobrinho, Gums' based delivery systems: review on cashew gum and its derivatives, Carbohydr. Polym. 147 (2016 Aug 20) 188–200. Available at: https://www.sciencedirect.com/science/article/pii/S0144861716301072.

[65] I. Lima, L. Moreno, S. Dias, D. Silva, A.C. Oliveira, L. Soares, R. Sousa, D. Dittz, H. Rolim, L. Nunes, Acetylated cashew gum nanoparticles for mesalazine delivery, Carbohydrate Polymer Technologies and Applications 5 (2023 Jun 1) 100265. Available at: https://www.sciencedirect.com/science/article/pii/S2666893922000809.

[66] R. Ghosh Chaudhuri, S. Paria, Core/shell nanoparticles: classes, properties, synthesis mechanisms, characterization, and applications, Chem. Rev. 112 (4) (2012 Apr 11) 2373–2433. Available at: https://pubs.acs.org/doi/full/10.1021/cr100449n.

[67] S. Deshpande, S. Sharma, V. Koul, N. Singh, Core–shell nanoparticles as an efficient, sustained, and triggered drug-delivery system, ACS Omega 2 (10) (2017 Oct 6) 6455–6463. Available at: https://pubs.acs.org/doi/full/10.1021/acsomega.7b01016.

[68] N. Wang, L. Shao, W. Lu, W. Fang, Q. Zhang, L. Sun, S. Gao, Q. Zhu, S. Chen, R. Hu, 5-aminosalicylic acid pH sensitive core-shell nanoparticles targeting ulcerative colitis, J. Drug Deliv. Sci. Technol. 74 (2022 Aug 1) 103578. Available at: https://www.sciencedirect.com/science/article/pii/S1773224722004890.

[69] V. Selvarajan, S. Obuobi, P.L. Ee, Silica nanoparticles—a versatile tool for the treatment of bacterial infections, Front. Chem. 8 (2020 Jul 15) 602. Available at: https://www.frontiersin.org/articles/10.3389/fchem.2020.00602/full.

[70] Y. Gao, D. Gao, J. Shen, Q. Wang, A review of mesoporous silica nanoparticle delivery systems in chemo-based combination cancer therapies, Front. Chem. 8 (2020 Nov 24) 598722. Available at: https://www.frontiersin.org/articles/10.3389/fchem.2020.598722/full.

[71] H. Tang, D. Xiang, F. Wang, J. Mao, X. Tan, Y. Wang, 5-ASA-loaded SiO2 nanoparticles-a novel drug delivery system targeting therapy on ulcerative colitis in mice, Mol. Med. Rep. 15 (3) (2017 Mar 1) 1117–1122. Available at: https://www.spandidos-publications.com/10.3892/mmr.2017.6153?text=fulltext.

[72] B. Moulari, D. Pertuit, Y. Pellequer, A. Lamprecht, The targeting of surface modified silica nanoparticles to inflamed tissue in experimental colitis, Biomaterials 29 (34) (2008 Dec 1) 4554–4560. Available at: https://www.sciencedirect.com/science/article/pii/S014296120800608X.

[73] A. Almatroudi, Silver nanoparticles: synthesis, characterisation and biomedical applications, Open Life Sci. 15 (1) (2020 Nov 19) 819–839. Available at: https://www.degruyter.com/document/doi/10.1515/biol-2020-0094/html.

[74] G. Kaur, S.K. Singh, R. Kumar, B. Kumar, Y. Kumari, M. Gulati, N.K. Pandey, K. Gowthamarajan, D. Ghosh, A. Clarisse, S. Wadhwa, Development of modified apple polysaccharide capped silver nanoparticles loaded with mesalamine for effective treatment of ulcerative colitis, J. Drug Deliv. Sci. Technol. 60 (2020 Dec 1) 101980. Available at: https://www.sciencedirect.com/science/article/pii/S1773224720312697.

[75] H. Agarwal, V. Shanmugam, A review on anti-inflammatory activity of green synthesized zinc oxide nanoparticle: mechanism-based approach, Bioorg. Chem. 94 (2020 Jan 1) 103423. Available at: https://www.sciencedirect.com/science/article/pii/S0045206819315020.

[76] M.M. Cortese-Krott, L. Kulakov, C. Opländer, V. Kolb-Bachofen, K.D. Kröncke, C.V. Suschek, Zinc regulates iNOS-derived nitric oxide formation in endothelial cells, Redox Biol. 2 (2014 Jan 1) 945–954. Available at: https://www.sciencedirect.com/science/article/pii/S2213231714000834.

[77] B. Klosterhalfen, C. Töns, S. Hauptmann, L. Tietze, F.A. Offner, W. Küpper, C.J. Kirkpatrick, Influence of heat shock protein 70 and metallothionein induction by zinc-bis-(DL-hydrogenaspartate) on the release of inflammatory mediators in a porcine model of recurrent endotoxemia, Biochem. Pharmacol. 52 (8) (1996 Oct 25) 1201–1210. Available at: https://www.sciencedirect.com/science/article/pii/0006295296004698.

[78] M. Navaei-Nigjeh, M. Gholami, M.S. Fakhri-Bafghi, M. Baeeri, M. Abdollahi, Molecular and biochemical evidences for beneficial effects of zinc oxide nanoparticles in modulation of chlorpyrifos toxicity in human lymphocytes, Iran. J. Pharm. Res. (IJPR): IJPR 17 (3) (2018) 927. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6094429/.

[79] M.H. Kim, H.J. Jeong, Zinc oxide nanoparticles suppress LPS-induced NF-κB activation by inducing A20, a negative regulator of NF-κB, in RAW 264.7 macrophages, J. Nanosci. Nanotechnol. 15 (9) (2015 Sep 1) 6509–6515. Available at: https://www.ingentaconnect.com/contentone/asp/jnn/2015/00000015/00000009/art00024.

[80] J. Li, H. Chen, B. Wang, C. Cai, X. Yang, Z. Chai, W. Feng, ZnO nanoparticles act as supportive therapy in DSS-induced ulcerative colitis in mice by maintaining gut homeostasis and activating Nrf2 signaling, Sci. Rep. 7 (1) (2017 Feb 24), 1-1. Available at: https://link.springer.com/content/pdf/10.1038/srep43126.pdf.

[81] M. Stewart, Mesalazine, Available at: https://patient.info/medicine/mesalazine-asacol-mezavant-octasa-pentasa-salofalk-zintasa, 2023.

[82] X. Li, C. Lu, Y. Yang, C. Yu, Y. Rao, Site-specific targeted drug delivery systems for the treatment of inflammatory bowel disease, Biomed. Pharmacother. 129 (2020 Sep 1) 110486. Available at: https://www.sciencedirect.com/science/article/pii/S075333222030679X.

[83] D.F. Li, M.F. Yang, H.M. Xu, M.Z. Zhu, Y. Zhang, C.M. Tian, Y.Q. Nie, J.Y. Wang, Y.J. Liang, J. Yao, L.S. Wang, Nanoparticles for oral delivery: targeted therapy for inflammatory bowel disease, J. Mater. Chem. B 10 (31) (2022) 5853–5872. Available at: https://pubs.rsc.org/en/content/articlelanding/2022/tb/d2tb01190e/unauth.

[84] C. Buzea, I. Pacheco, Toxicity of nanoparticles, in: InNanotechnology in Eco-Efficient Construction, Woodhead Publishing, 2019 Jan 1, pp. 705–754. Available at: https://www.sciencedirect.com/science/article/abs/pii/B9780081026410000281.

[85] Y.W. Huang, M. Cambre, H.J. Lee, The toxicity of nanoparticles depends on multiple molecular and physicochemical mechanisms, Int. J. Mol. Sci. 18 (12) (2017 Dec 13) 2702. Available at: https://www.mdpi.com/1422-0067/18/12/2702.

[86] S. Patnaik, B. Gorain, S. Padhi, H. Choudhury, G.A. Gabr, S. Md, D.K. Mishra, P. Kesharwani, Recent update of toxicity aspects of nanoparticulate systems for drug delivery, Eur. J. Pharm. Biopharm. 161 (2021 Apr 1) 100–119. Available at: https://www.sciencedirect.com/science/article/pii/S0939641121000540.