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REVIEW ARTICLE

Nanoparticle-Based Drug Delivery Systems: A Promising Approach for Targeted Ulcerative Colitis Therapy

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Abstract

Inflammatory bowel disease (IBD), includes ulcerative colitis (UC) and Crohn's disease (CD), is characterised by recurrent, chronic inflammation of the gastrointestinal system. For the treatment of UC, oral medication delivery to the colon is largely favoured since it increases their effectiveness while lowering systemic toxicity. To deliver oral a medication to the colon, which is at the distal end of the gastrointestinal system is however challenging, because of physiological difficulties, biochemical barriers and environmental obstacles, such as those brought on by mucus and epithelium. Recent preclinical studies have suggested that targeted medication administration to the colon using nanoparticle-based drug delivery systems (DDS) may be a promising strategy for the treatment of UC. Additionally, this study offers a thorough assessment of newly discovered naturally produced nanoparticles (such as extracellular vesicles and plant-derived nanoparticles) as well as DDS based on synthetic nanoparticles. These innovative UC treatment plans based on nanoparticles may present a chance for the clinical application of nanoparticle formulae.

Key words: Inflammatory bowel disease; Colitis, ulcerative; Crohn disease; Therapeutics; Nanoparticles; Drug delivery system.

Introduction

Chronic relapsing gastrointestinal (GI) tract illnesses referred to as "inflammatory bowel disease" are characterised pathologically by intestinal inflammation and epithelial damage.[1] Inflammatory bowel disease (IBD) might be classified the two primary categories: Crohn's disease (CD) and ulcerative colitis (UC). The terminal ileum is the area of the GI tract that is most frequently affected in people with CD (90 %): it is afflicted from the mouth mucosa to the anus.[2] Only the large bowel is often affected by UC; beginning in the rectum, eventually reaches the proximal colon. A tropism towards the appendix is also present in certain people with severe disease.[3, 4] IBD's aetiology is still poorly understood. Traditional treatments include immunosuppressive drugs for IBD including tacrolimus, methotrexate, ciclosporin-A, azathioprine and 6-mercaptopurine as well as anti-inflammatory therapies like corticosteroids and 5-aminosalicyclic acid.[5]

In recent years, the number of therapy options for IBD has considerably risen thanks to the development of monoclonal antibodies as biological treatments. The first biological to receive Food and Drug Administration (FDA) approval was infliximab, an antibody against tumour necrosis factor (TNF), to treat a severe, aggressive and CD fistulising[6] in 1998. After that, many TNF-antibodies, including adalimumab and certolizumab, have entered clinical trials and are now being developed for the treatment of IBD.[7] Other anti-

bodies that target molecules of adhesion, IL-12/IL-23, such ustekinumab and natalizumab, have also options for treating IBD have been proposed (Table 1).[8] As many patients do not react to the clinically authorised medications, such as TNF blockers and vedolizumab, there is still a significant unmet need for innovative treatment methods.[9-11]

Since the colon is the primary site of IBD, colon-targeted medication delivery devices have drawn a lot of consideration for IBD treatment. There are four basic categories into which the methods used in traditional medication administration may be divided: (1) techniques using coating polymers that are pH-dependent; (2) time-dependent techniques; (3) pro-drugs; and (4) polysaccharides. These methods have undergone in-depth research, as indicated in (Table 2)[8] and the FDA has given some of them the green light for use in clinical settings.

However, the specificity and release profile of these conventional colon-targeting strategies can vary; prior to the delivery mechanism reaches some of them release the colon medicine constantly in the digestive system, which reduces drug accessibility also raises the possibility of systemic negative effects.[12, 13] The requirement for innovative drug delivery methods that maximise drug absorption into an inflammatory colon while protecting healthy cells is highlighted by these shortcomings, hence minimising medication side effects.

The potential for treating IBD has increased thanks to the introduction of new technology. By using various processes, nanoparticles especially may be effective tools for delivering medications to certain locations inside the inflamed colon with precision (Figure 1).[14] DDS based on nanoparticles for medication delivery have a number of important benefits, including the fol-

Table 1: Inflammatory bowel disease (IBD) treatment based on monoclonal antibodies

Name of drug	Indications	Target site	Route of administrations
Infliximab (humans: 75 %; mice: 25 %)	UC and CD	TNF-α	Intravenous (iv)
(Humanised) **vedolizumab**	UC and CD	A4β7	Intravenous (iv)
100 % human osteokinumab	CD	IL-23 and IL-12	Intramuscular (im) injection
Golimunab (100 % human)	UC	TNF-α	Im injection
100 % human adalimumab	UC and CD	TNF-α	Im injection

UC: ulcerative colitis; CD: Chrohn's disease;

Table 2: Present drug delivery techniques for oral administration for inflammatory bowel disease (IBD) treatment approved by the Food and Drug Administration (FDA)[8]

Name of drug	Company name	The formulation	Mechanism of action
Aminosalicylate (5-ASA)	*Azulfidine*	5-ASA is azo-bonded to sulphapyridine. coating of 5-ASA with eudragit-S	Enzymatic reduction
	Asacol	Azo-bonds connect 5-ASA to 4-amino-benzoyl--alanine.	pH-responsive
	Colazal	Combining a pH-sensitive polymer coating and a polysaccharide coating	Enzymatic reduction
	CODES	The azo-bond-linked 5-ASA dimer 5-ASA is azo-bonded to sulphapyridine.	pH-responsive bacteria degradation
	Dipentum		Enzymatic reduction
	Salazopyrin		Enzymatic reduction
Budesonide	*Entocort EC*	Beads with ethyl cellulose matrix and edragit-L coating	Reactive to pH and time-dependent
	Uceris	Eudtagit-S covering a matrix core with multiple matrix system	Time-delayed and pH-responsive
Beclomethasone	*Clipper*	Tablet coated with eudtagit-L, 100-55	pH-responsive

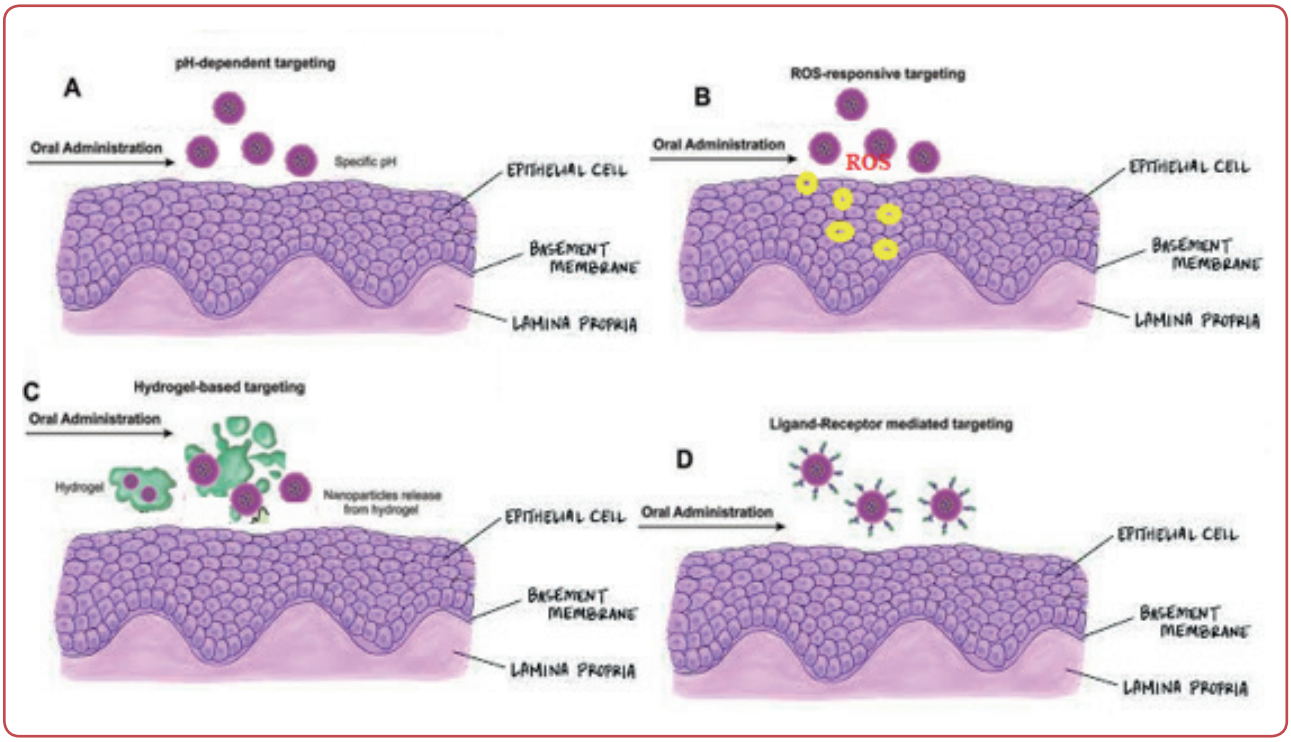

Figure 1: (A) After oral treatment, nanoparticles target the colon's irritated epithelium according to its particular pH. (B) After oral therapy, the colon's irritated epithelium is the target of nanoparticles based on the Reactivity of oxygen species (ROS) concentration present there. (C) A hydrogel is used to transfer nanoparticles to the colon's irritated after oral delivery. (D) Following oral therapy, a ligand and a nanoparticle interact to target to inflamed colonic epithelium.

lowing: In order to prolong pharmacological effects and maximise drug efficacy, there is a possibility for lowering dose regularity and minimise unfavourable systemic effects in IBD patients because they: (1) supply high local medication concentrations at the site of illness; (2) may lessen or stop medication effectiveness loss and degradation before it reaches the area of action; and (3) may stop or lessen medication effectiveness loss and degradation. These innovative nanoparticle-based UC therapeutic techniques may make it possible to introduce nanoparticle formulations into the clinic on a realistic level.

Nanoparticles

A nanoparticle (NP) is any material that is a particulate and has at least one dimension that is between 1 and 100 nm. They a variety of size-dependent characteristics and can be made up of one or many atom (or molecule) species.[12] Due to their vast size range, nanoparticles are able to reduce the energy state difference between tiny molecules and bulk materials.

Consider that a water molecule, one of the smallest of all molecules, has a diameter of around 0.3 nm, but the majority of viruses have a diameter between 20 and 400 nm and human cells typically have a diameter of 104 nm (Figure 2).[13] This comparison can help you better understand the nano-scale. The method employed for a nanoparticles creation has a significant impact on its size. Ultrafine particles have been created using the breaking down (top-down) method, which applies force to cut a solid into smaller pieces and the build-up (bottom-up) strategy, which builds gas or liquid molecules into nanoparticles by molecular transitions or molecule condensation.[14]

In contrast to their bulk counterparts, nanoparticles exhibit a number of distinctive characteristics, as well as different high surface-to-volume ratio (Figure 3),[15] thermal, mechanical, electrical, magnetically and optical characteristics as well as high surface energy. Nanoparticles are well suited for a variety of applications, including those in biology and medicine, due to these special char-

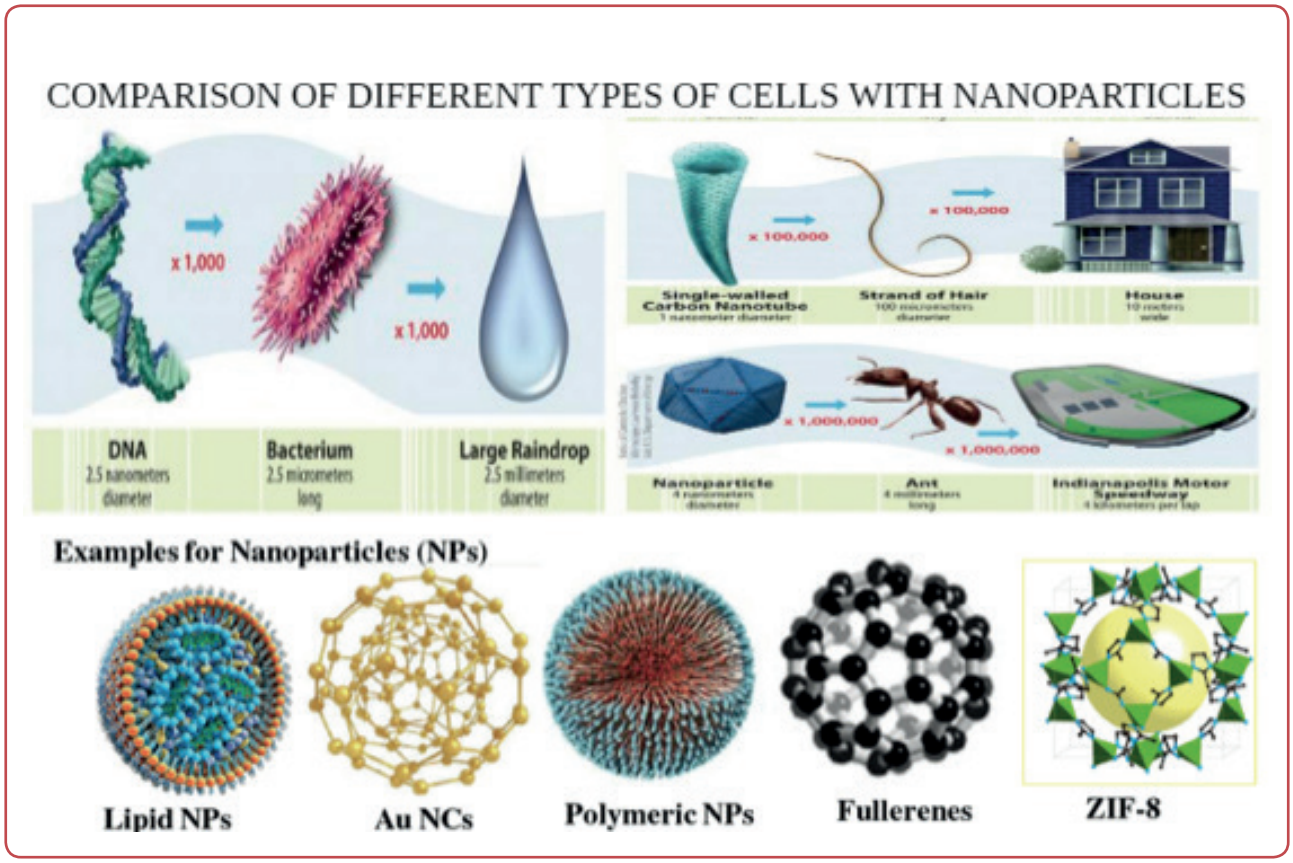

Figure 2: *Different types of nanoparticles based on their size*

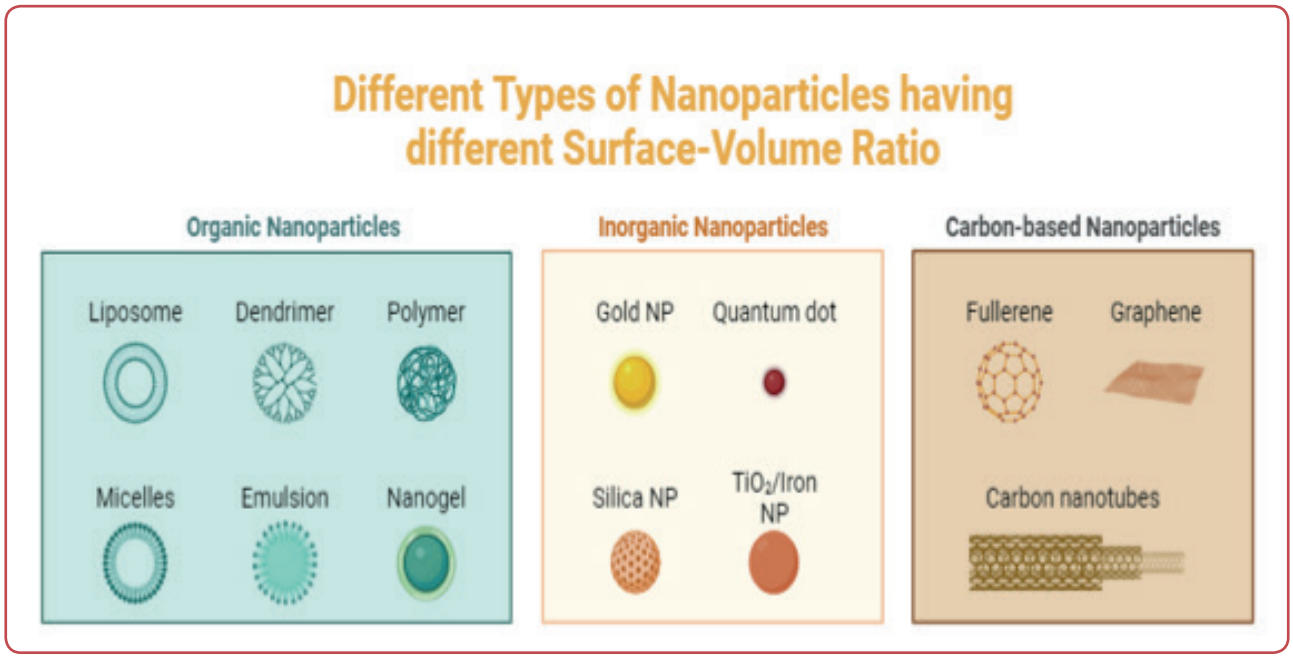

Figure 3: *Types of nanoparticles based upon their characteristics*

acteristics.[15-17] By adding appropriate functional groups to their surfaces, it is possible to control its dispersibility in various solvents and chemical reactivity, making them suitable for different applications.

General factors affecting delivering targeted drugs to the colon

Enzymes and pH

Orally given the nanoparticles in medication delivery must contend with the GI tracts at various pH levels and enzymatic activity also play a major as biochemical factors. Each section of the digestive tract has a unique pH, ranging from the colon's pH of 7-8, which is neutral, to slightly acidic (pH 1-3) stomach lumen needs somewhat acidic whereas duodenum and ileum requires for digesting.[18] Various pH levels may cause drugs to be sensitive to various reactions, such as oxidation, deamination, or hydrolysis, which might lead to a loss of function.[19] For instance, many peptide and protein-based medications, as well as medicines like erythromycin, penicillin and omeprazole, can be swiftly broken down by the stomach's severe acidity. There are also enzymes in the GI tract that can break down medicines, such as trypsin in the intestine, the stomach's pepsin and gastric lipase and salivary amylase within the mouth. More than 400 distinct kinds of aerobic and anaerobic microbes have been found in the colon.[20] Numerous hydrolytic and reductive metabolising enzymes are present in these bacteria and are in charge of degrading di-, tripolysaccharides.[21] As a result, medications that target the colon are routinely delivered via polysaccharides like chitosan, guar gum and pectin.

Mucus

The first physical barrier that drugs taken orally must get past is the mucus layer.[22] The hydrogel complex in mucus made up of inorganic salts, bacterial waste, lipids, proteins (including antibodies) and carbohydrates.[23] The basis of mucus' barrier properties is its intricate web of negatively charged, heavily glycosylated segments of its mucin filaments. Mucin also includes domains that repel water that are evenly spaced and have a high affinity for binding hydrophobic particles.[24] Although many tiny and big medicinal molecules cannot be delivered orally due to mucus, encapsulating these medications into possibly, nanoparticle carriers increase oral bioavailability of the substance.[25] Whether a medication is able to enter and enter epithelial cells is determined by the carrier's capacity to interact with mucus. Nanoparticles that are ingested can penetrate the mucus and remain attached to strongly adhering mucus or reach the intestinal epithelium. They can also attach to mucus that is weakly adhered and stay there unless the mucus is removed firmly adherent mucus and remain there until the mucus is cleared, or both.

Epithelium

The stomach is incapable of absorbing drugs due to its harshly acidic environment and enzyme content.[26] The intestinal epithelium, which is made up of several cell types and structural elements, is very absorbent. Intestinal villa's epithelium is mostly made up of enterocytes and goblet cells. While permitting the digestion of dietary materials, enterocytes regulate the flow of large molecules and infections.[27] The mucus gel layer is secreted by goblet cells and is made up mostly of mucins, which are high-molecular weight glycoproteins suspended in an electrolyte solution. In addition, M cells, which are present inside the epithelium of Peyer's patches, are composed of enterocytes and a few goblet cells. Tight junctions, which are made up of claudins, occludins and junction adhesion molecules and firmly bind these cells, create a solid barrier that prevents chemicals and pathogens from passing through.[28] The intercellular gaps' very small surface area and the close closeness of the connections between epithelial cells, transport via the paracellular pathway is constrained under healthy conditions.[29] IBD, particularly UC, may alter intestinal permeability, facilitating easier passage of nanoparticles over epithelial barrier in the intestine.[30] Nanoparticles are transported across cells by a process called transcytosis, in which cells take the particles up. Endocytic activity starts this off at the apical membrane of the cell. Nanoparticles are released at the basolateral pole, where they may interact with immune cells in the submucosal layer, follows their passage through the cells. However, due to enterocytes' poor endocytic activity, this route's transport efficiency is often quite low. The size, zeta potential, surface hydrophobicity and presence of a ligand at the particle surface, in addition to the physiology of the GI tract, the animal model used and other factors, all have an impact on the transport of nanoparticles by this pathway.[31]

Bump in efflux of P-glycoprotein (P-gp)

Bump in efflux of P-glycoprotein, a transporter for escape membrane, functions as an ATP-dependent drug efflux bump at the apical surface of cells.[32] In order to prevent hydrophobic substrates from entering the cytoplasm, P-glycoprotein might function as a hydrophobic agent however, removing them from the lumen and returning them to the extracellular media. Beta-adrenoreceptor blockers, calcium channel blockers, steroid hormones, immunosuppressants and cardiac glycosides are some examples of these hydrophobic substrates. The high expression of P-glycoprotein in small intestinal epithelial cells points to the significance certain proteins in regulating a drug's oral bioavailability when taken orally.[33] For instance, a lot of anticancer medications, P-glycoprotein substrates, such as vincristine and paclitaxel, shouldn't be administered orally.[34]

Microbiota

The microbiota has an impact on the GI tract's physiological processes, from maintaining local barrier homeostasis to regulating metabolic, inflammatory response, immunology and other activities on a systemic level.[35, 36] The anaerobic colon is where the big intestinal microbiome is most commonly found. Here, it gets its energy from digesting several substrates, including di-, tri- and mucopolysaccharides, which were not broken down in the small intestine. To utilise this roughage as a source of carbon, the anaerobic bacteria develop a broad spectrum of reductive and hydrolytic enzymes. They react by detecting a variety of substrates and producing the required digestive enzymes in response to the complex carbohydrate combination that enters the colon.[37] Drug delivery methods can thus contain prodrugs and biodegradable polymers that will be specifically broken down by the microbiota's enzymes. The biodegradable polymers used in nanoparticle-based drug delivery systems, such as naturally occurring ring polysaccharides derived from plants, animals, algae and microbes are transformed into simple saccharides by the colonic microbiota.[38, 39] Redox potential, a gauge of all microbial and metabolic activity, may be altered by the varied microbiota, which is especially remarkable.[40] As a result, a very specific method for colon-targeted medication administration might be exploited to take advantage of variations in redox potential caused by the microbiota.

Use of synthetic nanoparticles to target colon systems

Drug delivery techniques based on synthetic nanoparticles, recently developed, shown characteristics that make them appropriate for oral colon medication administration.[41] Pharmaceuticals can be directly delivered to regions of inflammation using nanoparticles, which can get beyond physical barriers. These nanoparticles are capable of dissolving, trapping, or encapsulating the active component (a medication or physiologically active chemical), making them useful as drug carriers in therapeutic settings. Active chemicals can also attach themselves to nanoparticles or soak onto them. Nanoparticle delivery techniques have several benefits over traditional colon-targeted treatments, including increased effectiveness, less toxicity and better bio-distribution.[42] This section examines the various methods for delivering targeted medications to inflamed colon tissue using orally given nano-delivery devices for UC (Figure 1).

Nano-delivery systems that depend on pH

To further increase the stability of medicines taken by mouth, nanoparticles sensitive to stimuli have been created. Examples of materials used to make pH-sensitive nanoparticles include anionic polymers and acrylates, which dissolve and/or swell at higher pH levels but are insoluble at lower pH levels.[43] Because of their complexity to pH, these nanomaterials may be able to hold onto and perhaps preserve their payload in the stomach and small intestine's acidic environment while still releasing the medicine in the colon's higher pH.[44, 45] Many pH-sensitive polymers have been utilised to create solid dosage forms that are gastro-resistant, examples of which include now on the market and have been shown to be safe.[46] Methacrylic acid copolymers (*Eudragit*) are the pH-dependent coating polymers most frequently utilised for oral administration. The pH at which they are soluble can change depending on how the side chains are made.[46] For instance, methacrylate and lactic and glycolic acid polymer hybrid (*Eudragit S100*) mixes were used to create pH-sensitive nanoparticles that were filled the use of budesonide (BSD), a corticosteroid that is actively localised. At neutral and acidic pH levels, these nanospheres demonstrated powerful drug release capabilities. That was pH dependant, with a period of persistent release takes place at pH 7.4.

BSD-loaded nanospheres were found to be more therapeutically efficient than BSD alone in studies on animals employing a TNBS-induced model of colitis. *In vivo* tests with these nanospheres revealed a more and stronger focused adherence to the inflammatory and ulcerated rat mucous colonic tissue than conventional enteric-coated microparticles. They also had decreased systemic toxicity.[47, 48] Additionally, drug release from liposomes coated with *Eudragit S100* was noticeably reduced in solutions that mimicked the pH conditions of the stomach (pH 1.4) and small intestine (pH 6.3), but was equal to uncoated control at pH 7.8, showing that this liposome formulation exhibited suitable pH responsive release characteristics. Bile salts presented an extra challenge to the coating layer, which suggests that this stability may be negatively impacted *in-vivo*, leading to early liposome disintegration and drug release in the duodenum.[49] The SPL-Pred-MCM mesoporous silica nanoparticle system is another intriguing pH-responsive nanosystem.[50, 51]

ROS-responsive nano-delivery systems

Clinical success in the treatment of UC may also be demonstrated by drug carriers that react to changes in redox potential.[52] An imbalance between the production of reactive oxygen species (ROS) and the decline in antioxidant defence mechanisms is known as oxidative stress.[53] Due to the high levels of ROS produced by inflammatory cells like neutrophils and macrophages, oxidative stress is a distinctive feature of inflammatory processes.[54] UC has been linked to excessive ROS production. For instance, in biopsies collected from the sites of people with UC compared to those without, mucosal ROS concentrations are 10- to 100-fold greater and ROS concentrations correlate with disease development.[55] Redox-responsive nano-delivery systems have a lot of potential for IBD therapy since they take advantage of the pathological aspects of the disease. Thioketal nanoparticles (TKNs) may be taken orally and are employed to deliver TNF- siRNA to areas of intra- nasal inflammation. The polymer poly-1, 4-phenyleneacetone dimethylene thioketal (PPADT), which is preferentially destroyed in response to ROS, is the source of TKNs.[56] Enhancing TNF-siRNA transfection stability, mucosal transit, cellular internalisation and endosomal escape requires complexing TNF-siRNA with cationic species like DOTAP. A cationic lipid called 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) can combine with TNF-siRNA to generate DOTAP/siRNA. When TKNs were given orally to a mouse model of UC, the abnormally high amounts of ROS that were present in the areas of intestinal inflammation caused them to be destroyed. As a consequence, TNF-mRNA levels in the colon were reduced; protecting animals against UC and siRNA targeting the proinflammatory cytokine TNF- was released.[57] Similar to this, nitroxide radical-containing nanoparticles (RNPo) were created for the transport of low-molecular weight TEMPOL. They are made of an amphiphilic block copolymer called methoxy-poly(ethylene glycol)-b-poly (4-[2,2,6,6-tetramethyl-piperidine-1-oxyl]oxymethylstyrene (MeO-PEG-b-PMOT). These particles specifically accumulated in the colons of animals with colitis after being given to them orally. This copolymer's hydrophobic portion has persistent nitroxide radicals that may scavenge ROS, which raises the possibility that RNPo could play a significant role in the treatment of UC. The application of ROS-responsive systems has been constrained despite the fact that they represent a promising strategy for treating UC.[58, 59] These barriers include (1) the instability of the drug delivery carriers in the harsh, acidic and enzyme-rich environment of the upper GI tract; (2) premature release, which lowers the drug concentration at inflamed colon sites and results in undesirable side effects; and (3) the ability to target on specific cell types. Future research should aim to create multifunctional delivery systems that employ several delivery mechanisms (for example, both pH and ligand-receptor interactions) and/or that react to various ROS in order to reduce these issues.

Nano-delivery systems based on hydrogel

Enhancing therapeutically active compounds activity, reducing their negative effects and preventing early degradation are the main objectives in the development of drug delivery systems. Ideally, controlled-release systems can fulfil these requirements by minimising dose and delivery frequency while keeping drug concentrations within a therapeutic window over a lengthy period of time.[60-63] in several areas of medicine, including IBD, hydrogels are a very alluring kind of drug delivery mechanism.[64] A cross-linked polymer network plus a significant amount of water make up hydrogels. Because hydrogels have a high-water content (usually 70 %–99 %), they have good biocompatibility and may easily encapsulate hydrophilic medicines due to their physical similarities to biological tissues. Furthermore, since most hydrogels are created in aqueous solutions, there is little chance that they would denaturise

or aggregate when exposed to organic solvents, which can happen to drugs like recombinant proteins and monoclonal antibodies.[65] It was discovered that a recently created hydrogel was sensitive to the environment of the colon because it used the ions (Ca^{2+} and SO_4^{2-}) to cross-link chitosan and alginate.[66] Nanoparticles bearing the anti-inflammatory tripeptide Lys-Pro-Val (KPV) were enclosed in this hydrogel. The particles could transit through the stomach and small intestine while being protected by the hydrogel and they were precisely broken down in the inflammatory colon. In a DSS model of colitis, the use of these enhanced NPs in a hydrogel system greatly decreased colitis symptoms, which was followed by a decrease in myeloperoxidase (MPO) activity and histologic changes. In addition, a dosage 1200-fold lower than free KPC in solution was effective in reducing mucosal inflammation *in vivo*. IBD was also treated using hydrogel-embedded nanoparticles that contained CD98 siRNA.[67] by reducing CD98 expression in mice colonic mucosa and reducing DSS-induced colitis, CD98 siRNA/polyethyleneimine (PEI) nanoparticles coated in this hydrogel were administered orally. This hydro-gel technique produced great results, according to a second investigation.[68, 69]

Targeting-reliant active

The active targeting of nano-delivery systems purposeful homing of NPs to inflamed or diseased locations may produce more precise spatial localisation and boost a drug's therapeutic efficiency while reducing its side effects on healthy tissue.[70] When an NP has a ligand on its surface, it may more easily attach to certain molecules that are over expressed on the surface of target cells, leading to receptor-mediated endocytosis.[71] The parenteral route of administration has been the focus of the majority of research on active targeting-dependent nano delivery systems, which target a variety of illnesses including cancer, infections and inflammation.[72, 73] The application of this tactical technique for orally given nano delivery systems was made possible by the successful findings of this study. To increase the effectiveness of oral administration and therapeutic results, several ligands have been added to nano delivery carriers.[74, 75] Certain ligands/receptors are over expressed on the surfaces of various cells (such as immune cells and colonic epithelial cells) during the inflammatory phase of UC and may thus serve as molecular targets for anchoring drug delivery systems through particular interactions.[76] For instance, in the inflamed state of UC, the expression of the glycoprotein CD[98] is elevated on immune cells (such as macrophage cells) and colonic epithelial cells.[77, 78] These ligands have often included sticky proteins like lectins and monoclonal antibody fragments as well as saccharides (such as mannose, galactose and hyaluronic acid).[71, 79]

Naturally derived nanoparticles for colon targeting

Despite having some preclinical success, synthesised to treatment for UC, nanoparticles have two significant drawbacks. Before using these nanoparticles in clinical settings, each component's potential *in vivo* toxicity must be assessed. In addition, the manufacture of these nanoparticles is on a small scale. The drawbacks of synthetic nanoparticles may be solved by natural nanoparticles, which are regarded as secure and affordable. Recent preclinical studies have demonstrated considerable preliminary potential for treating UC using nanoparticles generated from edible plants and extracellular vesicles (EVs) synthesised from mammalian cells.[80, 81] These results imply that a novel strategy for treating UC may be offered by naturally occurring nanoparticles. The creation naturally, of produced Applications of nanoparticles in the therapy of UC will be outlined in this section.

Axonomical vesicles

Axonomical vesicles (AVs) have been recognised as significant cell-to-cell communication mediators over the past 20 years, enabling the functional transfer of bioactive chemicals across cells. As a result, it is becoming more and more obvious that these vesicles play a role in the aetiology of several human illnesses, opening the door to potential therapeutic uses.[82]

AVs may be described is secreted by the cell, attached to phospholipid bilayer entities that might be discovered in body fluids and are produced by an evolutionary mechanism that has remained constant across time. Too far, all kinds of human cells have been tested to release AVs.[83] Exosomes, microvesicles and apoptotic vesicles are the three subtypes of AVs that can generally be distinguished based on morphological, biochemical and genetic information characteristics. When a cell is apoptosing, the plasma membrane produces vesicles, which are then separated into many

membrane-enclosed vesicles from the contents of each cell. In comparison to exosomes (50-150 nm) and microvesicles (100-1000 nm), apoptotic vesicles are frequently larger particles (1–5 m). Which include cytoplasmic organelles and fragmented nuclei. The latter exhibit not just a somewhat overlapping size distribution but also extremely comparable biogenesis mechanisms.[84] Microvesicles are created by the outwards splitting and fusing of the plasma membrane, whereas exosomes are created via the exocytosis of multivesicular bodies. This is the primary distinction between their methods of production. Certain subgroups of proteins, mRNA and non-coding RNA, are abundant in both exosomes and microvesicles. Despite the fact that their contents probably differ from extra chromosomal DNA has also been found in certain known EV forms.[85]

Patients with IBD may benefit from the therapeutic potential of naturally produced immunosuppressive EVs. A good example of this is the immunosuppressive action of EVs generated by transforming growth factor beta 1 (TGF-1)-high intestinal epithelial cells (IECs).[86] These EVs preventing the development by of colitis generating immunosuppressive dendritic cells (DCs) and regulatory T cells in mice with colitis brought on by dextran sulphate sodium (DSS). These results suggested that gut immunological homeostasis is maintained in part by EVs from IECs. Exosomes produced by bone marrow-derived DCs that have received interleukin-10 (IL-10) treatment may also be able to inhibit colitis brought on by TNBS. Further research revealed that the advantages of IL-10 exosomes for treatment were pertaining to IL-2, IFN and TNF mRNA expression being down regulated in colon tissue while IL-10 mRNA was up regulated, as well as the over expression of regulatory T lymphocytes in the lamina propria of the colon.[87] According to EVs were effective nano-vehicles for transporting biological agents for the treatment of IBD, according to these findings.

The goal of medical regeneration is to rejuvenate the body's deteriorating, harmed and lost tissues and cells.[88] The use of mesenchymal stem/stromal cells (MSCs) obtained from adipose, bone marrow and cord blood to treat tissues affected by various clinical diseases are of significant interest. MSCs' capacity to move to wounded locations, encourage functional recovery and alter immunological reactions is their main therapeutic benefits.[89] Recent research has demonstrated that EVs released by MSCs can be used as therapeutic agents to treat tissue damage, including colitis.[90] As a result, MSC- EVs were anticipated to develop into a more effective cell-free therapeutic strategy that might circumvent the challenges related to the usage of natural or modified stem cells. In a study looking into it was determined whether EVs from bone mesenchymal stem cells (BMSCs) decreased the severity of TNBS-induced colitis by reducing the levels of NF-Bp65, TNF-, iNOS, COX-2 and IL-1 mRNA and protein and expanding the expression of IL-10.[91] BMSC-EVs containing various proteins, mRNAs and microRNAs were also found to have this effect. Additionally, it was shown that Human umbilical cord mesenchymal stem cells (hucMSCs) exosomes might lessen the severity of DSS-related colitis by up regulating IL-10 and down regulating TNF-, IL-1, iNOS, IL-7 and IL-6 expression.[92] Combined, these intriguing findings suggest which MSC-EVs may one day replace complete cells in regenerative medicine due to their theoretical benefits over intact MSCs.[93, 94]

Plant derived nanoparticles

There is a tremendous deal of curiosity in how plant-derived nanoparticles might contribute to interspecies communication and directly ameliorate human illnesses, particularly intestinal inflammation.[95, 96] Intestinal stem cells were discovered to take up grapefruit nanoparticles (GELNs) that were ingested orally and included proteins, lipids and microRNA.[97, 98] In addition, these nano particles appeared resistant to being broken down by saliva, the stomach's acidic environment, both the extremely proteolytic enzymes that are active and are located in the digestive tract. These findings demonstrated that plant-based nanoparticles that are edible might be absorb and supplied to the gut orally, where they might exert effects like intestinal regeneration.[99, 100] For the treatment of digestive tract patients disorders like IBD, edible plant-derived nanoparticles with anti-inflammatory characteristics and natural targeting of colonic tissues may constitute a unique natural and nontoxic delivery technology that is simple to scale up.[101-104]

It has been discovered that GDNs, or grapefruit-derived nanovesicles, are preferentially absorbed and by intestinal macrophages that they help mice with colitis brought on by DSS.[105,106] Intestinal macrophages' increased synthesis re-

duced production of IL-1 and TNF and increased haem oxygenase-1 (HO-1) served as a conduit for the anti-inflammatory effects of GDNs. Because These GDNs were demonstrated to be stable across a broad pH range, biocompatible and biodegradable. It is possible that they may be utilized to create fresh oral medication administration methods. For instance, the therapeutic advantages of the anti-inflammatory medicine methotrexate (MTX) against DSS-induced colitis in mice were increased when the drug was added to GDNs were significantly improved above those of no cost MTX. These findings showed that GDNs can promote intestinal macrophage homeostasis and function as immunological modulators in the colon. Consequently, these nanoparticles might to be used as oral medication delivery vehicles for small molecules that might lessen inflammatory reactions in illnesses of humans.[107]

Traditional medicine has made use of ginger as a digestive aid. 6 shogaol and 6 gingerol, which contain anti-inflammatory, antioxidant and anticancer properties, are two of the most therapeutically useful components of ginger.[82] Recently, we discovered that administering chemicals derived from ginger as nanoparticles perhaps a more successful method for targeting colon tissue than ingesting a plant or taking a pill.[108, 109]

The diameter of the ginger-derived nanoparticles (GDNPs) used in our prior research is about 230 nm. We found that these GDNPs effectively target the colon and were mostly absorbed by cells that line the inner layer of the intestinal tract, the site of inflammation associated with IBD. In animal models of IBD, GDNPs may include considerable amounts of the bioactive elements of ginger, substantial quantities of lipids, certain proteins, 125 miRNAs and other molecules.[110, 111] Macrophages and intestinal epithelial cells (IECs) are the principal receptors for GDNPs, which are harmless. In colitis models, oral GDNP administration increases IEC survival and proliferation, decreases pro inflammatory cytokine (TNF-, IL-1 and IL-6), further boosts anti-inflammatory cytokine (IL-22 and IL-10) concentrations, indicating showed GDNPs can reduce risk factors while enhancing therapeutic outcomes. The non-toxicity and affordability of ginger are among its benefits by using ultrasonic dispersion, high-speed centrifugation and a blender to separate juice of ginger into individual pellets, ginger root is transformed into GDNPs. Additionally; GDNPs prevent chronic colitis and acute colitis, as well as cancers linked to colitis.[112, 113]Additionally, the fragments facilitate intestinal healing by boosting the continuation of proliferating colon lining cells while concurrently reducing the generation of proteins that trigger inflammation these results suggest that innovative, natural delivery methods for the treatment and prevention of IBD may be provided by plant-derived nanoparticles.[114, 115] The drawbacks associated with synthesised nanoparticles and their possible dangers, such as their small manufacturing size, may also be solved by these plant-derived nanoparticles.

Future perspective

The possibility for treating IBD using drug delivery methods based on synthetic nanoparticles, extracellular vesicles and plant-derived nanoparticles has been discussed in this study. A completely selective medication delivery method that targets the area of inflammation in UC has advanced significantly.[116] However, by directing drug-loaded nanoparticles to the small intestine (an additional location of this illness), as well as the large intestine, nanotechnological techniques might potentially be used to Crohn's disease. The need to (1) specifically release nanoparticles from the hydrogel to the small intestine and/or (2) decorate the nanoparticles with ligands specific to receptors expressed mostly in epithelial cells of the small intestine are two challenges to targeting and retaining nanoparticle-loaded drugs in this organ. Currently, our team and others are looking on delivery methods that might target and transport medicines laden with nanoparticles to the small intestine. To maximise therapeutic efficacy while minimising negative effects, a therapeutic NP-based system should aim its payload directly at the inflamed location.[17, 117] To improve the targeting of NPs, a variety of targeting modalities can be utilised, including ultrasound-assisted administration and micro-needle-based systems.[110, 111] In animal models, inflamed vasculature may be targeted with precision using biomimetic nanoparticles that replicate the natural inflammation-targeting mechanisms of human immune cells such as neutrophils, platelets and macrophages.[118, 119] These biomimetic nanoparticles combine the specific functions of biological components with nanoengineering's capacity to efficiently transport therapeutic medicines. This strategy might be used for IBD tailored distribution.

Smart nanoparticle-based delivery systems that have the ability to serve both therapeutic and diagnostic purposes (ie "nanotheranostics") for IBD should also be taken into consideration. Complex nanoparticle-based delivery systems can work in the theranostic environment by concurrently offering diagnostic and therapeutic capabilities, perform multimodal imaging, or distribute more than one medication to develop combination treatments.[120] Upon detecting modifications in physiology or the illness state, new and more complex nano-system designs that react to pH variations and the enzymatic environment can become bioactivatable. In this situation, medication release might be triggered by a variety of characteristics related to the IBD microenvironment. In the future, programmable drug release and even more complex nanoparticle designs may be possible thanks to the utilization of external triggers like light or applied electro-magnetic fields. Nanoshells,[121] dendrimers,[122] liposomes,[123, 124] and nanogels[125, 126] have all demonstrated the potential to be excellent for these kinds of applications. This is because they have imaging characteristics and can act as nanocarriers.[127-131]

Conclusion

Unfortunately, a number of obstacles might prevent successful clinical use of nanotheranostics. Researchers should work to develop a thorough knowledge of interactions between nanoparticles and IBD as well as the possibility of collaboration between diagnosis and treatment in order to solve the possible problems. Additionally, more work has to be put into the large-scale synthesis of nanotheranostics, the evaluation of their long-term toxicity and the development of pertinent regulatory protocols. Only then can we possibly provide this innovative technology for efficient and customised therapy to the patient's bedside.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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