Review Article

Smart nanocarriers: A novel tool for the treatment of ulcerative colitis

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ABSTRACT

Colitis nanotherapeutics are quickly succeeding and are utilized to sort out numerous restrictions of conventional drug delivery systems such as drug targeting and non-specific distribution with reduced oral bioavailability. Advancement in medical science has put into novel strategies for targeting approaches that may converse new anticipate for ulcerative colitis patients. Numerous beneficial nanocarriers have been commending for clinical use. Nanocarriers have been intended for finest size and surface characteristics to improve their targeting for desired site. Using the pathophysiology of colitis, as an identification marker, their improved permeability and retention effect nanotherapeutics are able to hold loaded active drug to colitis site. In addition, side effects of drugs can also be conquer or reduced using nanocarriers. These nanocarriers are now being vigorously investigated and are on the perspective as the latest generation.

Keywords: Ulcerative colitis, novel drug delivery system, smart carrier, drug targeting, sustain release

INTRODUCTION

Inflammatory bowel disease is autoimmune, relapsed, chronic disease. The IBD has two types, ulcerative colitis (UC) and Crohn's disease (CD). In case of UC, inflammation can occur only in colon site, whereas in CD inflammation can occur in any part of digestive system might be from mouth tract to rectum.[1] The colitis suffered patients almost have a notably thinner mucus layer. Conventional available treatments are failed to control the disease symptoms effectively in number of patients, unfavorably distressing quality of life. This is happening due to the non-targeted delivery of drug moiety. Therefore targeted carriers are required with maximum effect of drug.[2] Using various novel carriers system [Figure 1], targeted drug delivery could be possible. The review article provides perception on the use of nanocarriers as an elemental tool in colitis management. Here, we focus on the characteristics and types of nanocarriers, how nanocarriers are being used as drug delivery systems to decrease the inflammation more safely and effectively and also to reduce the side effects.

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VARIOUS CARRIERS BASED DRUG DELIVERY SYSTEM

Nanofiber-based drug delivery

Oral administration of conventional drugs is most preferred and favored route over the parental administration. Due to the presence of gastric secretions, all types of drugs cannot be administered by oral route. However, targeted drug delivery is not possible with conventional drugs. The specific targeted drug delivery has a capability to diminish unwanted effects and to increase the pharmacological effect.[3] With the broadcasting of nanotechnology, researchers have become more attentive in studying the exclusive properties of nanosized material. Electrospinning technique has been widely accepted as flexible and easy method for nanofiber fabrication from the polymer solution. Natural or synthetic polymers are fabricated into nanofibers. By providing the electric field on the tip of nozzle, electrospun nanofibers are prepared. Electrospun nanofibers have extensive appliance in pharmaceutical field including nanosensors, wound dressing, filtration, drug delivery, and cosmetic mask. From

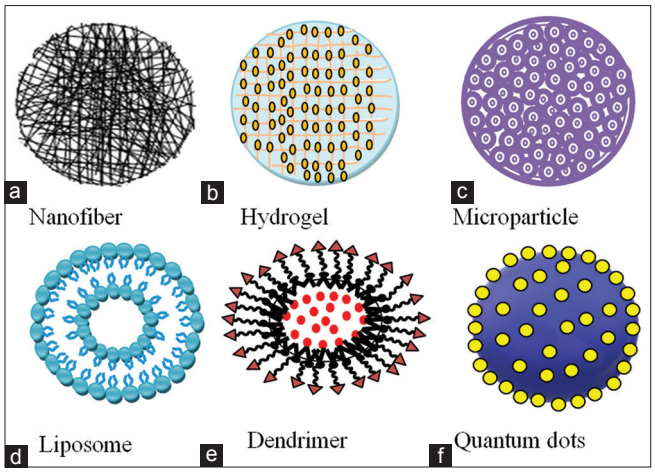

Figure 1: Types of nanocarriers for drug delivery. (a) Nanofiber: Polymeric ultra-thin fiber in which drugs are conjugated to or encapsulated in polymers. (b) Hydrogel: A macromolecular polymer gel with cross-linked polymer chains in which drugs are encapsulated (c) microparticle: Small spherical particle drug is dissolved, entrapped, or encapsulated to microparticle matrix. (d) Liposome: Self-assembling structures composed of lipid bilayers in which an aqueous volume is entirely enclosed by a membranous lipid bilayer. (e) Dendrimer: Synthetic polymeric macromolecule of nanometer dimensions, which is composed of multiple highly branched monomers that emerge radically from the central core. (f) Quantum dots: Semiconductor nanocrystal, drug is entrapped in polymers

these all applications, drug delivery is most efficient era for drug delivery due to the promising features such as simple process, high loading capacity, better encapsulation efficiency, stability, and simultaneous delivery of different therapies.[4] Drug-loaded electrospun nanofibers are stable, easy to prepare, appropriate for the sustained, as well as control release formulations. Besides of this, the electrospinning is beneficial technique for poorly water-soluble drugs to improve the solubility as well as dissolution rate. Recent research on UC using nanofibers carrier.[5,6] The hydrogels are made up of supramolecular scaffold nanofibers consisting of anti-inflammatory drugs and glycopeptides. These prepared nanofiber provides delayed release of drug. The SEM results signify that MP loaded, EL100, ES100, and MAE100 nanofibers might be prepared using electrospinning method.[6] The prepared nanofiber with enteric coated polymer:drug ratio reveals no MP release in small intestine region. The results imply that polymer Eudragit S-100 (polymer/drug ratio: 10:0.5) scaffold nanofibers have a potential role in delayed release delivery system for MP. Nanofibers approach can be consider as an inexpensive, simple, and efficient method for the formation of delayed release drug delivery system. A group fabricated nanofibers of indomethacin prepared for colonic drug delivery in UC.[7] The whole study concluded that by choosing an suitable experimental-based strategy and optimization practice that can be fruitfully applied for the formation of nanofibers build on Eudragit polymers to attain colonic drug delivery. The formulation having ES:ERS (60:40) and drug:polymer ratio of 3:5 reveals suitable characteristics and protected the drug from upper GI tract and provides safe release in colonic drug delivery system for indomethacin. Same study has been conducted including fabricated sulfobutyl ether β-cyclodextrin that provides considerable strengthened nanofibers without the loss in bioactivity of the nanofiber.[8] The PD/NFs-CDs gel has the potential use for the treatment of UC. The fabricated nanofiber TXG was efficient in satisfying DSS-induced UC mode.[9] The studies employing liquid HR-FE-TEM and SEM revealed nanofiber nature of TXG. Atomic force microscopy of TXG revealed a slender, rectilinear, and rod-like structure with diameter of mean length of 640 ± 360 nm and 2.3 ± 0.5 nm diameter. TXG improved the cell viability in DSS-induced cytotoxicity IEC-6 cell line.

Hydrogel-based drug delivery system

Oral and intravenous drug administration is preferably commonly used routes for drug administration, mucosal membrane bid admirable alternatives, by virtue of through entrée to the blood stream, high permeability with minimum overdose risk with maximum possibility of attaining local treatment. The biggest challenge in oral drug delivery system is the partial retention time at the site of mucosal tissue.[10] This kind of issue can be conquering by the use of various mucoadhesive polymeric materials as a drug carrier with cross linker. Numerous research reports show enhanced efficacy of drug carriers based on mucoadhesive in rectal drug delivery for the treatment of various colonic diseases.[11] Mucoadhesive drug delivery systems offer reduction of migration of the drug in the colon by prolonging the drug residence time. In contrast to the oral administration, rectal route mucoadhesive-based drug delivery systems enhance drug absorption as well as bioavailability.[12] Various research groups demonstrated their work,[13] research group developed a carrier that is thermosensitive, in this polymer-based carrier that is liquid at the room temperature but upon contact with body temperature turns in to viscous gel. Followed by rectal administration to mice with dextran sulfate sodium-induced colitis model, the system carrying mesalamine or budesonide becomes which becomes enough viscoelastic near by the body temperature, as shown in Figure 2. Nanocarrier containing drug given to mice put on more weight and had decreased biologic and histological characteristic of UC than the platform alone or liquid drugs through enema convinced to the mice.

Image analysis cleared that enemas delivered with and without the platform reached same distances in the colons of mice, but superior colonic retention was attained using the platform.[14] Research group developed a hydrogel which is inflammation targeting (IT-hydrogel) based system for colon inflammation. IT-hydrogel microfibers were loaded with corticosteroid dexamethasone (Dex) (anti-inflammatory) which were stable, released drug simply during enzymatic digestion and adhesion to inflammation site. *In vitro* and *vivo* in two colitis models. Dex-loaded IT-hydrogel enemas, apart from not free Dex enemas, administered each other day to mice with colitis outcome in a considerable decrease in inflammation and were concerned with lower Dex peak concentrations of serum and therefore minimum systemic drug exposure. *Ex vivo* investigation of colon tissue samples from UC site confirmed that IT-hydrogel microfibers remain preferentially attached to inflammation cell mucosa evaluated with normal histological sites. In another study, Zhai *et al.*[15] prepared a hydrogel system based on ascorbyl palmitate (AP) and incorporated a model drug (fluorescently-labeled dextran) into the hydrogel system. This research group reports that this hydrogel system can be shaped

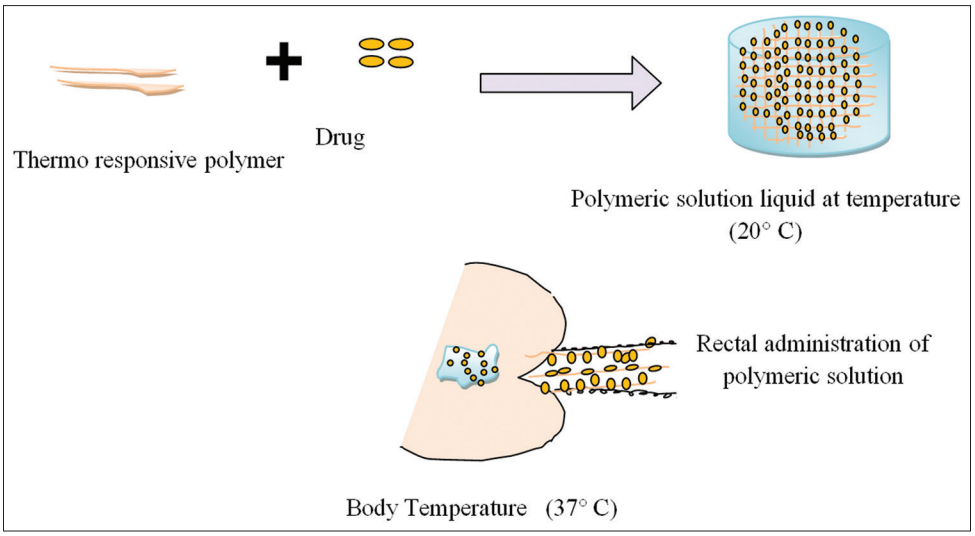

Figure 2: Hypothesis drug delivery to colonic inflammation site by administration of hydrogel through rectal route. The polymer-based carrier that is liquid at room temperature but turn in to viscous gel as reached body temperature 37°C

in a moderate environment. The hydrogel system demonstrated a shear-thinning behavior. AP hydrogel system released near about 60% of the drug in 5 h and illustrated realistic cytotoxicity profile. The AP hydrogel system tackles the discharge of FD4 and its permeability across intestinal Caco-2 cells, followed by rectal delivery. The study has confirmed that AP hydrogel system has potential for specific local delivery of macromolecules to the colon inflammation in UC.

The research group prepared poly (N-isopropylacrylamide) (NiPAAm)-based thermo gelling and cross-linking polyamidoamine (PAMAM) macromers were synthesized and merge to produce a sprayable, *in situ* gel forming dual hydrogel system for delivery of hydrogel coatings onto warm tissues.[16] Cell viability was enhanced when delivered by a dual stream spraying method because of decreases in pressure, viscosity, and the effects of micronetwork formation in a turbulent stream. The result confirmed that sprayable in cell-loaded thermoresponsive hydrogel coatings provides promise as novel drug delivery system for the treatment of UC.

Enema as rectal-based drug delivery system

Oral administration of drugs for UC shows systemic toxicity, this is happen due to the non-targeted delivery of drug to the inflammation site. Enemas are liquid preparation inserted directly to the rectum for the specific delivery of active moiety to the desired site.[17] First, the main drawback of enema preparation is a trained person who is required for proper administration; second, leaking from rectum is also possible; third, it may cause stain to cloths as well as uncomfortable for the patient.[18] By various research groups, a variety of activities has been demonstrated. Research groups concluded that collected data file the efficiency of rectal infusion of *Lactobacillus reuteri* ATCC 55730 in recovering colon inflammation in children with active UC also modifying the mucosal expression levels of a few cytokines which are responsible for inflammation. Stain of *L. reuteri* ATCC 55730 alone having the ability to decrease the inflammation as equivalent in terms of effectiveness as compared with conventional anti-inflammatory drugs.[19] This stain could be used a long-term basis is able to preserve such effectiveness in UC by rectal infusion. Budesonide enemas and foams have also been used for the treatment of UC. It has been found to be effective and better tolerated because of low bioavailability with minimum effects on plasma level, therefore reducing the steroid effect.[20] The drug is absorbed in hemorrhoid plexus and distal rectum[20] and the two randomized trials compared rectal budesonide and mesalamine in active UC and mesalazine was confirmed to be superior than budesonide. The very first studies by research group of enema having budesonide drug 2 mg/100 mL become to be as effective and better tolerated as 5-ASA enema for treatment of proctitis and active UC.[21] Both enemas provide considerable progress in histopathology and endoscopy as well in clinical sign (quality of stool, movement of bowel per day, presence of mucus, and blood). Although the rate of clinical remission at 4 weeks on 38% for patients was treated with budesonide enema, 60% for those treated with 5-aminosalicylic acid enema ($P = 0.03$). The most recent trail by research group of Hartmann and Stein[22] evaluated the therapy with mesalazine enema (4 g/60 mL) and budesonide enema (2 mg/100 mg) in an open randomized study with 237 patients with active mild-to-moderate left-sided UC. Clinical remission rates of 60% and 75% were accomplished after 8 weeks of treatment with rectal or budesonide or mesalazine, respectively ($P < 0.02$). After these findings, authors concluded that mesalazine enema was related with a appreciably superior remission rate, which was also maintain by previous finding data of endoscopic and histological remission.

Microparticles as a carrier

Local targeting of drug is the biggest challenge for the treatment of UC. For enhanced localization of drug, a well-designed drug delivery system strategy is required for beneficial to enhance therapeutic efficacy. Microparticulate system is one of the best approaches for controlled drug delivery in specific site of inflammation. Microparticles could be best approach for colon targeting. Microparticle size range of 5–15 μm provides localization of drug,

ultimately increases the residence time of drug in the colonic region. Particle size of this range is able to adhere at the site of inflammation, finally provide maximum release of drug at colonic pH with maximum pharmacological action.[23] Microparticles consisting of natural, semi-synthetic, and synthetic polymers prepared to enhance bioavailability. These delivery systems provide plentiful benefits contrast to conventional formulations, which offered improved bioavailability, reduced toxicity, improved patient convenience, and compliance.[24] Microparticles are prepared by various research groups, the research group has developed embelin loaded guar gum microparticles by using emulsification technique. The *in vitro* release of the optimized formulation was found to be 88.5 ± 3.8% in 24 h, have shown extremely sustained and delayed the release of embelin at a specific colon site. Average particle size of embelin-loaded microparticles showed 12.9 ± 0.75 μm. This microparticles system produced less side effect as compared to conventional drug formulation. The study demonstrated the application of the microparticulate system in enhancement of stability and controlled release of drug. By another group, Nidhi *et al*.[25] prepared embelin-loaded microspheres (F1) formulation consisted of 1:1:0.3 w/w/w EC:ES100:embelin ratio using 2% Span 80 for stabilization might delivery of drug specifically to colon. The drug release is pH and time-dependent base system. This approach fabricates time-dependent and pH-dependent sustained release of drug as compared to other conventional formulations. This study inspects the application of microparticulate system for enhancing stability and controlled release with effective results concerning the beneficial efficacy. An another study demonstrated that, chitosan-coated particles are capable in delivering mesalamine to targeting site. *In vivo* study showed that mesalamine-coated microparticles have potential to maintain the concentration of mesalamine in the colonic site for a longer period of time, ensure the efficiency of treatment, and reduce the frequency of administration as well as improve patient compliance. The study prepared microspheres by the ionic-gelation emulsification method using tripolyphosphate as cross-linking agent. The microspheres were coated with pH-based polymer Eudragit S-100 by the solvent evaporation method so that drug release in the stomach can be avoided.[26] It was examined that Eudragit S-100 coated chitosan microspheres gave maximum drug release in the colonic site. Eudragit-coated chitosan microspheres were capable carriers for colon-targeted delivery of mesalamine. Apart from this, chitosan microsphere using drug mesalamine. Mesalamine is quickly absorbed from region of small intestine, so it is mandatory to formulate a colon-specific drug delivery system. Chitosan microspheres were used for this purpose prepared by an emulsion-solvent evaporation based on a multiple w/o/w emulsion. Microspheres showed 0% in pH 1.2 after 2 h, max. 20% in pH 7.4 after 3 h, and near 60% in pH 6.8 after 8 h looks appropriate for site-specific delivery of mesalamine *in vitro*.[27]

Liposomes as carrier for colon drug delivery

However, at present, regular attempts have been taken for scheming of colon-specific drug delivery systems with enhanced site specificity and flexible drug release kinetics to achieve various therapeutic requirements. Liposomal drug delivery system receiving a considerable attention for delivery of therapeutic agents in UC.[28] Liposomes are basically sphere-shaped vesicles consist of one or more phospholipids bilayers. The previous results of liposomes ensured that systems can target inflamed tissue.[29] Various activities has been assessed on liposome. In this study, liposomes have showed better deposited in inflammatory site offers enhanced effect. With the help of thin film hydration method by using cholesterol and Phospholipon® 90G as polymers.[30] Liposomes were successfully formulated with optimized concentrations. *In vivo* and *ex vivo* study demonstrates *ex vivo* and *in vivo* study confirmed more drug deposition in inflammatory colonic site from the liposomal formulation. Therefore, this would be capable tool for releasing the active moiety, particularly in inflammatory colonic site for effective treatment of UC. Locally administration of cationic liposomes based complexed with IL-10 and IL-4 genes was predictable to decreases the inflammation in patients UC and avoid harmful systemic side effects. Reactive oxygen species have a key role in pathogenesis of UC.[31] Cationic liposomes enhance the uptake and residence time of superoxide dismutase (SOD) and the SOD mimics tempamine by colonic cells *in vitro* and in *ex vivo* models. Anionic liposomes were capable to deliver SOD, catalase, and tempamine to inflammation rat mucosa and attained longer residence time and improved uptake for specific treatment of UC.[32] Carnitine-loaded liposomes were capable to precise butyrate metabolism in colonocytes in a DNBS-induced rat colitis model.[33] These liposomal formulations are capable to impede local oxidative stress and decrease colon inflammation. Tirosh prepared liposomes that accumulate, privileged in the inflammation mucosal site of rats that were provoked with experimental colitis, subsequent luminal administration.[34] Protein investigation of inflammation mucosal specimens, extracted at pH 3, 5, and 7, exposed an amplified expression of transferrin (TF) at acidic pH 3. The liposomes with negatively charged stick to both commercial and mucosal TF at lower pH, but not at neutral pH. It is concluded that, at a low pH, typical of the colon lumen in UC, TF mediates gave mucoadhesion of negatively charged liposomes to the inflammation site. Research by Poh and his team prepared a folate-targeted liposome that is capable to deliver active agents to inflammation site in colitis. These folate-targeted liposomes are warranted for the targeted drug delivery to inflammation site.

Dendrimer as a carrier

Dendrimers are polybranched, tree-like polymers, synthetic, polyfunctionalized, macromolecules with specific size, shape, and chemical functionality, having capability to deliver the drug to specific sites. The unique properties and multivalent structure make them striking for applications in medicine. Along with the various medical possessions of dendrimers that have been prepared over the past decades, the anti-inflammatory properties of a number of groups of dendrimers are nearly all recently discovered. Dendrimer molecule has hundreds of sites to pair to an active moieties.[36] Various studies have been conducted for the management of UC using the dendrimer as carrier. Prepared dendrimer has anti-inflammatory and antioxidant property. The G5-NH-Ac-TOS conjugate could be a prospective choice for the treatment of UC in clinic as well as pathologies related to oxidative stress and inflammation.[37] Dendrimer glucosamine (DG) having anti-inflammatory property confirmed by measuring the release

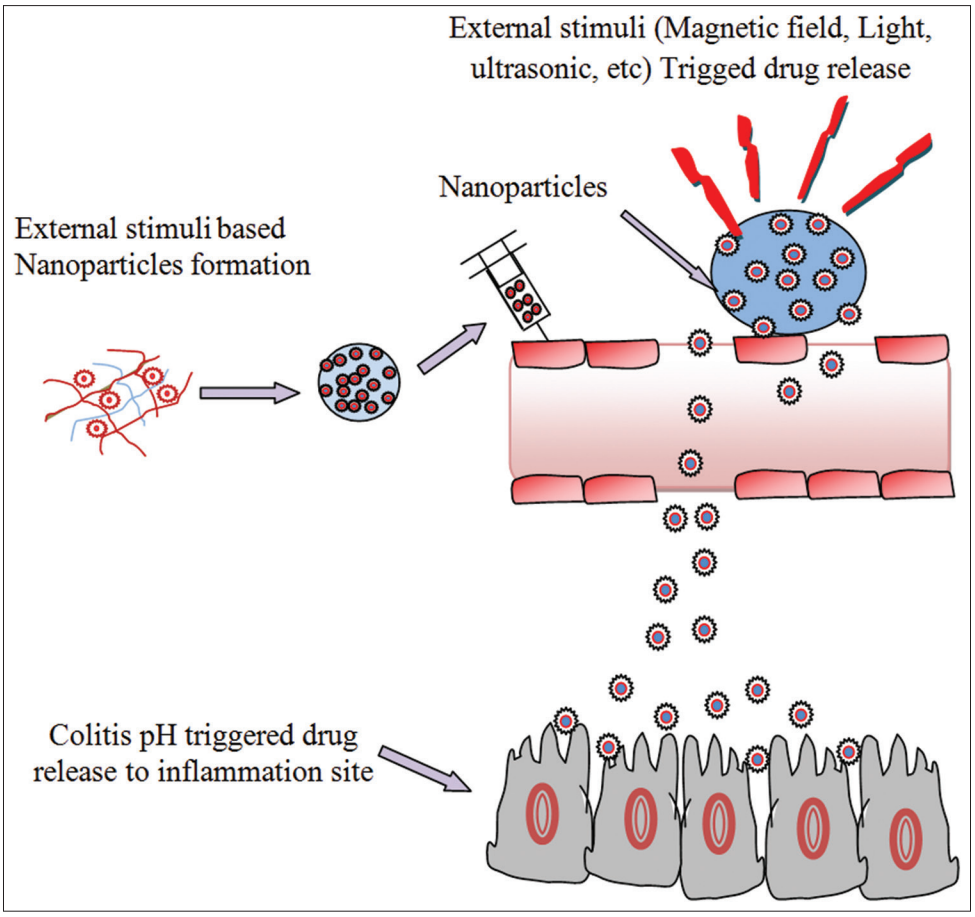

Figure 3: Light-responsive system (1) injecting nanoparticle through parental route (2) application of external stimuli like light, ultrasound (3) release of drug from the nanocarriers at inflammation site

of pro-inflammatory cytokines IL-6,IL-8, and TNF-α by various immune cells stimulated during 21 hrs by Salmonella minnesota lipopolysaccharide (LPS). DG 30 min earlier to LPS activation or DG was added 2 or 4 h after the start of activation by LPS. In these all experimental settings, DG inhibited the LPS-mediated release of pro-inflammatory cytokines by total peripheral blood mononuclear cells with 50% inhibitory concentration (IC_{50}) of 6.8 ± 1.1 μm.[38] ABP dendrimer has immunomodulatory and anti-inflammatory properties, either effect directly on monocytes or by activation of the immune cells. Even though the cause of dendrimer ABP endures to be dispute in *in vivo* models of inflammation, phosphorus-containing dendrimers may represent a immunologically active drugs for the management of UC.

Simple surface-functionalized PAMAM dendrimers conjugated with indomethacin, an NSAID. These novel formulations gives anti-inflammatory effect. This ensures the reduction of inflammation in colitis.[39]

Quantum dots as carrier

Quantum dots are nanocrystals or tiny particles of a semiconducting material such as indium arsenide, cadmium sulfide, and silicon. QDs are used for *in vitro* and *in vivo* imaging, which are expected to be important tool for diagnoses of many diseases, the understanding of lymphocyte immunology and embryogenesis. Only limited data have been for QDs during the search.[40]

The prepared QD shows improvement in DSS colitis model. The level of inflammatory markers has become normal. The results were confirmed that 1L-1,TNF-α, and MPO conjugated to QDs can detect these inflammation markers. The application of this QD to estimate the inflammation.[41]

Light and magnetic responsive nanoparticles as carrier

Light-responsive system signifies a means to drug release at specific target with the external light illumination [Figure 3]. The contact of 1 time or repeatable light irradiation with photosensitive carriers leads to achieve the on-off drug release. The stimuli by magnetic approach offer non-invasive method for temporally and spatially.

With the various stimulus like external magnetic field, the magnetic nanoparticles shows drug release response. The huge surface ratio of MNPs gives plentiful active sites for conjugation of biomolecule, allowing gaining their proposed smart functions by providing

a localized external magnetic field, as target specificity with inflammation site. Moreover, when these MNPs were encapsulated in colloidal carriers, such as solid nanoparticles, liposomes, and micelles. The basic structures might turn into sensitive to an external magnetic field to grasp multifunctional formulations for both therapeutic and diagnostic purposes.[42,43]

FUTURE DIRECTION

Even though nanomedicine is a fairly new stem of science, its conversion into disease care has been swift. The sole characterization of nanoparticle drug carriers crafts them well suitable for colon applications. Nanocarriers are formed for treatment of most colitis, more clinical data are required. This can as well help in recognizing the finest relevance for colitis. Thus, further intricate targeted systems, which can release drugs at a target site of inflammation when exposed to external stimuli such as and temperature and light, are also beneath expansion. Together with the progression of nanocarriers drug delivery systems, move forward in nanoscale imaging recommend the potential for the development of multifunctional "smart" nanoparticles that may make possible release or drug in colitis patient.

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