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Colon targeted drug delivery system: Recent approaches.

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Abstract:

The reduction in the systemic toxicity along with high efficiency of local drug delivery for the diseases of colon (crohn's, ulcerative colitis, bowel disease, colon cancer) can be achieved by targeting the colon for drug delivery. Factors such as pH, bacteria, mucus barrier and transit time which affect the efficacy and delivery of the drug, must be considered while developing the targeted drug delivery system. The conventional ways of drug delivery to the colon has its own challenges and obstacles. Thus, the active research area for colon targeting is nanotechnology-based delivery of drugs. Nanotechnology has shown promising results like reduced toxicity, localized drug delivery, improved efficacy and high accumulation in the infected area. But these are also associated with limitations such as uptake of the drug in the upper part of the intestine, entrapment by mucus, variations due to pH, drug degradation by acid/enzyme and burst phenomenon. These compromises the therapeutic efficacy of the novel system. To prevent these obstacles, advancements in the technology of the drug delivery is needed which can provide high therapeutic efficiency. This review tries to explain the conventional methods of colon drug delivery along with the challenges associated with it. The role of novel drug delivery systems and its advances in colon targeting has been discussed along with the future prospects.

Keywords: Colon, Novel delivery, Oral therapeutics, Dual stimuli, Mucoadhesive, Recent advances

Introduction

The prevalence of the colonic disease has increased worldwide in the last few decades, urging the effective treatment strategies of colonic disorders for safe and efficacious drug therapies [1]. The oral drug delivery system is perceived as the most convenient delivery system because of its efficacy and non-invasive process [2]. Thus, oral-based drug delivery system to the colon is a focal point significant to treat varied confined sicknesses such as Ulcerative Colitis (UC), crohn's disease, inflammatory bowel syndrome, and Colorectal Cancer (CRC) [3]. Among colonic infections, Colorectal Malignant Growth (CMG) has caused the most malignant related fatalities in Europe, and is the world's third most diagnosed cancer [1,4]. Even in low-incidence regions such as Asia, the prevalence of Inflammatory Bowel Disease (IBD) is also rising at an alarming rate [5]. Therefore, effective diagnosis and treatment have thus become a major concern in the healthcare sector. The colon-based drug delivery frameworks are built to release the medication specifically into the upper GI tract to the Pulm-monary area without the premature release rate.For the effective advancement of a colon-based delivery system, it is crucial to understand the physiological characteristic of the colon microenvironment encompassing disease site. As the GI tract experiences dynamic changes in the motility, pH and enzymatic action, from the stomach to the digestive system [6]. Colon targeted delivery systems are being actively followed for the local treatment of the colon diseases, since non-targeted conventional therapy may have adverse effects and fewer efficacies due to the absorption of the drug through the systemic route before reaching the targeted site of action [7, 8]. Some of the advantages of the colon based delivery system are shown in Figure 1.

This review portrays a portion of the physiological and obstacles looked by orally managed conveyance frameworks in colon-specific disorders, and the ongoing advancements in orally regulated colon-focused on novel drug delivery system along with the commercial preparations and future research directions in this domain.

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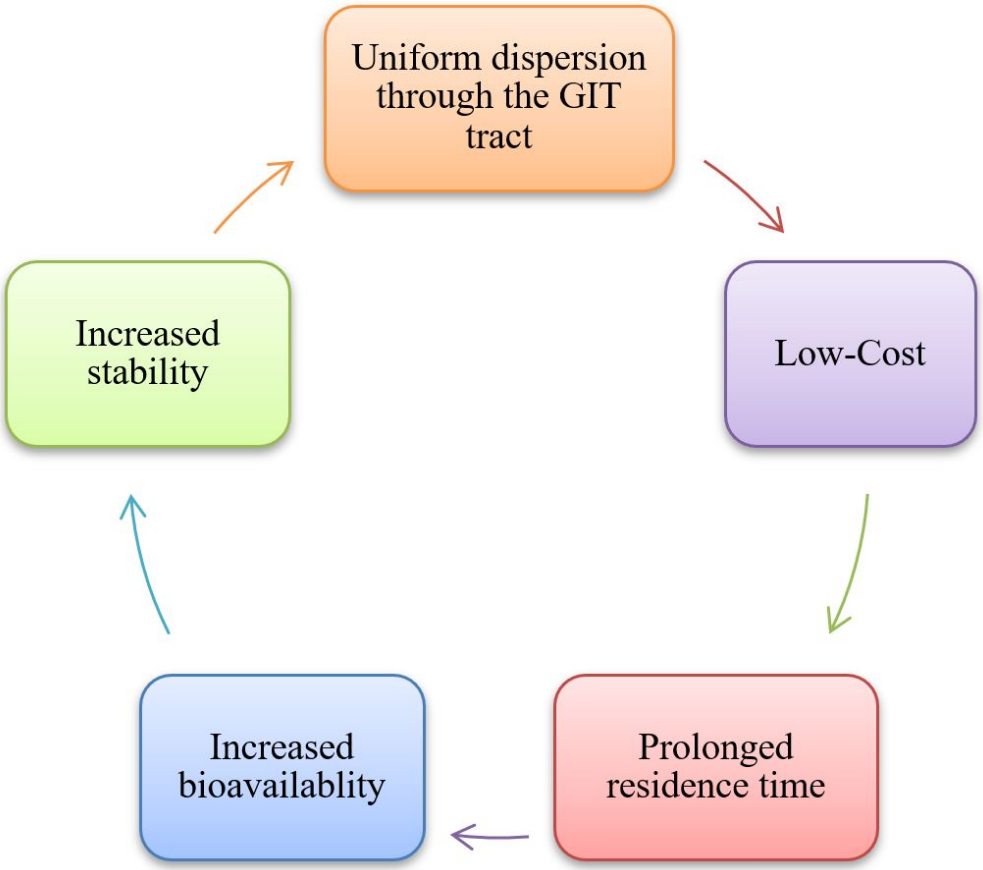

Figure 1: Merits of Colon targeted drug delivery system

2. Conventional treatment and challenges

The micro flora of the colon is progressively perceived as an ideal activating portion in the structure of colon delivery system, as the sudden increment of the microscopic organisms' population and relating catalyst actions in the colon shows a non-linear occurrence of the GI transit time. The colon comprises over 400 distinctive bacterial species with a population around 1011-1012 CFU/ mL with Bacteroides, Eubacterium, Lactobacillus, and Bifidobacterium preceding other species to a larger extent [9]. The enzymes accountable for polysaccharide degradation includes -L-arabinofuranosidase, D-xylosidase, D-fucosidase, D-galactosidase, and, D-glucosidase [10]. Polysaccharides are present in the dietary sources and the host produced fluids are the major source of the energy and carbon for such bacteria's [11]. Conventional techniques for the treatment of colon-specific diseases include administration of drugs through the parenteral, rectal and oral routes. The parenteral delivery route shows rapid effects of medication as it avoids the first pass metabolism but unwanted undesirable side effects may occur due to the distribution of medication all over the bodyIn addition, rectal route delivers the drug to a distal colon and prevents systemic absorption [12]. But rectal delivery route leads to non-compliance effects to the patients which can sometimes affect therapy. Medication utilized for intrarectal route of administration is provided as suppositories, solutions and foams. The intrarectal course is utilized as a method both for the systemic delivery and for the conveyance of topically active medication to the intestine. Corticosteroids, for example, prednisolone and hydrocortisone are directed by the means of the rectum for the treatment of ulcerative colitis [13]. The oral course is the most preferred and desired approach to regulate the drugs for the colon-specific ailments [14]. The colon is accepted to be an appropriate assimilation site for peptides and protein drugs for the accompanying reasons. Less variety of enzymatic components and similar proteolytic action to the colon mucosa is substantially less than that is seen in the small digestive tract. It also protects the peptide drugs from enzymatic degradation and hydrolysis in the jejunum/duodenum and in the end discharges the medication into the ileum or colon which prompts more prominent fundamental bioavailability [15]. Commercial marketed preparations [16] for the various treatment of colon based disorders are shown in Table 1.

Formulation	Drug	Company	Disease	Side effects
Mesacol tablet	Mesalamine	Sun pharma, India	Ulcerative colitis	Flatulence, Hair loss, Headache
Mesacol enema	Mesalamine	Sun pharma, India	Ulcerative colitis	Rectal discomfort, Stomach pain
Asacol	Mesalamine	Win-medicare, India	Ulcerative colitis, crohn's disease	Stomach upset, vomiting
Intazide	Balsalazide	Intas, India	Ulcerative colitis	Joint pain, Vomiting, Respiratory tract infection
SAZO	Sulphasalazine	Wallace, India	Ulcerative colitis, crohn's disease	Headache, Loss of appetite, Nausea
Lomotil	Diphenoxylate HCL, atropine sulphate	RPG Life, India	Mild ulcerative colitis	Red or swollen gums, dry mouth, nose, or throat
Buscopan	Hyoscine butylbromide	German Remedies, India	Colonic motility disorder	Dry mouth, abnormal sweating
Cyclominol	Diclomine	Neol, India	Irritable colon syndrome	Nausea, Sleepiness, Dizziness, Blurred vision
Colospa	Mebeverine	Solvay, India	Irritable colon syndrome	Nausea, Vomiting, Rash, Headache, Heartburn and indigestion
Entofoam	Hydrocortisone acetate	Cipla, India	Ulcerative colitis	Nausea, Vomiting, Headache
Normaxin	Clidinium bromide	Systopic labs, India	Irritable colon syndrome	Confusion, Sleepiness. Weakness, Dizziness, Blurred vision
Pro-banthine	Propenthline bromide	RPG Life, India	Irritable colon syndrome	Dry mouth, dizziness, sweating
Eldicet Spastic colon	Solvay, India	Pinaverium bromide	Irritable colon syndrome	Stomach pain, Diarrhea, Nausea, Vomiting

Table 1: Marketed Formulations related to colon drug delivery system.

Regardless of the upsides of colon-specific oral medication conveyance, obstacles, for example, acidic and enzymatic degradation and systemic delivery from the small digestive tract could lead toantagonistic effects and lesser bioavailability at the infection site [17, 18]. Some of the hurdles in colon-specific drug delivery system are mentioned in figure 2.

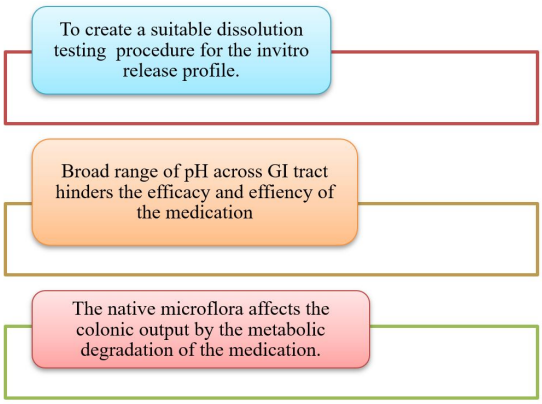

Table 1: Challenges in colon based drug delivery system.

3. Considerations in the drug delivery to colon

The differences in the nature and characteristics of absorption, physiology and anatomy of the gastrointestinal tract along with drug release site and dosage transit kinetics must be considered in the targeting of colon drug delivery. In addition, there should be consideration of significant variations of both types of gastrointestinal tracts i.e. diseased and healthy [19]. Improved in vivo and in vitro evaluation of the dosage forms can only be achieved, when there is prior understanding of the environment of the gastrointestinal tract. Thus, there is a need to discuss some of the factors (pathological and physiological) that are playing important roles in the design and delivery of the drug to the colon system as shown in figure 3.

3.1 pH

The values of pH ranges from 1 to 8 in different regions of the gastrointestinal tract. As shown in Figure 1, stomach lies in acidic region (1-3 pH) while the environment of small intestine ranges from acidic to neutral (5.9-7.8 pH) [20,21]. This colonic pH triggers the delivery of some drugs to the colon, thus making it an important aspect of colon drug delivery. This pH dependent drug delivery can prevent the drugs degradation in the stomach's acidic environment, by utilizing of polymers like Eudragit S100 for the coating of the drug which remains stable at this pH [22]. However, the variability in intra individual and inter individual pH values are some of the main issues of pH dependent delivery of drugs. Also, in patients of crohn's and colitis show lower values of colonic pH, making the efficiency of pH dependent delivery of drugs uncertain [23].

3.2 Colonic microflora

The colon of human comprises of more than 300

These bacteria utilize hydrolytic and reductive enzymes to degrade polysaccharides which are required for their energy [25]. The behavior of the dosage form and the drug can be stimulated with the help of unique environment provided by the bacterial species. Thus, polysaccharides and prodrugs like pectin, guar gum and chitosan are more likely utilized in the delivery to the colon, as these are degraded to drug upon the action of bacterial enzymes [26,27]. However, drug metabolism by bacteria can cause toxicity or inactivity. In addition, drug, diet and disease can also induce the fluctuations of colonic microflora [28]. These findings reflect that these conditions can alter the release of the drug formulations based on bacterial enzymes, which should be taken into consideration when designing a drug delivery specific to the colon system.

3.3 Transit time

Delivery systems that are dependent on time utilize transit time of gastrointestinal tract as an approach for colon targeting [29]. The transit time ranges from 6-70 h and 2-6 h in colon and small intestine respectively [30,31]. The patients of colitis have shown transit time faster than others [32] while there is a reduction in the transit time of the formulation in case of patients of bowel disease [31]. This reduction of the transit time can lead to the reduced efficiency of the therapeutic agents as the exposure duration of the agents to the diseased sections is reduced.

3.4 Mucus barrier

Mucus is a layer of hydrogel comprising of glycoproteins rich in mucin. It hinders the drugs absorption in the gastrointestinal tract [33,34].The layer of human mucus contains basal layer, a thinner and a luminal layer with the thickness ranging from 10-200 μm [35].The basic roles of the mucus consists of protection of epithelial cells from pathogens and mechanical harm along with chyme lubrication [34].The mucosal layer leads to poor therapeutic action of the drug as the adhesive property of the mucus binds the drug to its surface which is eliminated only in faecal matter. This limits the duration of delivery of drug to the site of action [36].

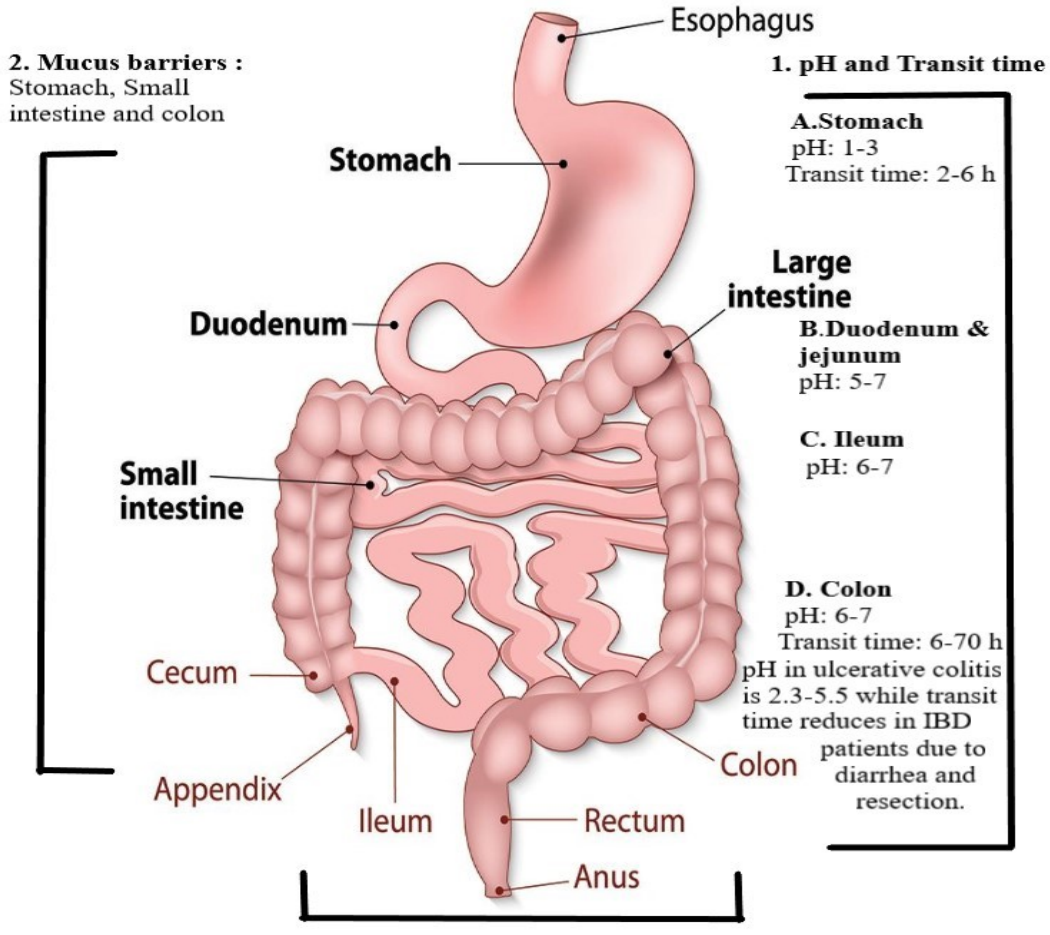

Figure 3. Considerations in colon targeted drug delivery.

4. Novel drug delivery system for colon targeted drug delivery

The drawbacks associated with conventional dosage forms can be combated with the application of novel drug delivery systems. Nanotechnology based delivery systems provides several advantages such as they can escape from the hurdles associated with conventional oral systems and also provides large area for gastrointestinal interaction (Figure 4) [37]. The efficacy of the treatment and uptake of the cells are influenced significantly by the surface, shape and size of nanoparticles [38,39]. The carrier size plays a critical role in the delivery of the drug to the colon. The effect of enhanced permeability and retention enables the maximum accumulation of the small sized carrier into the tissues of the colon [40]. Further, the effect of off-targeting can be avoided by modifying the surface of nano-carriers by conjugating them with ligands or antibodies, so that they only bind specifically to the target receptor or antigen. [41]. Thus, the potential of novel drug delivery systems is tremendous and promising in delivery to colon systems.

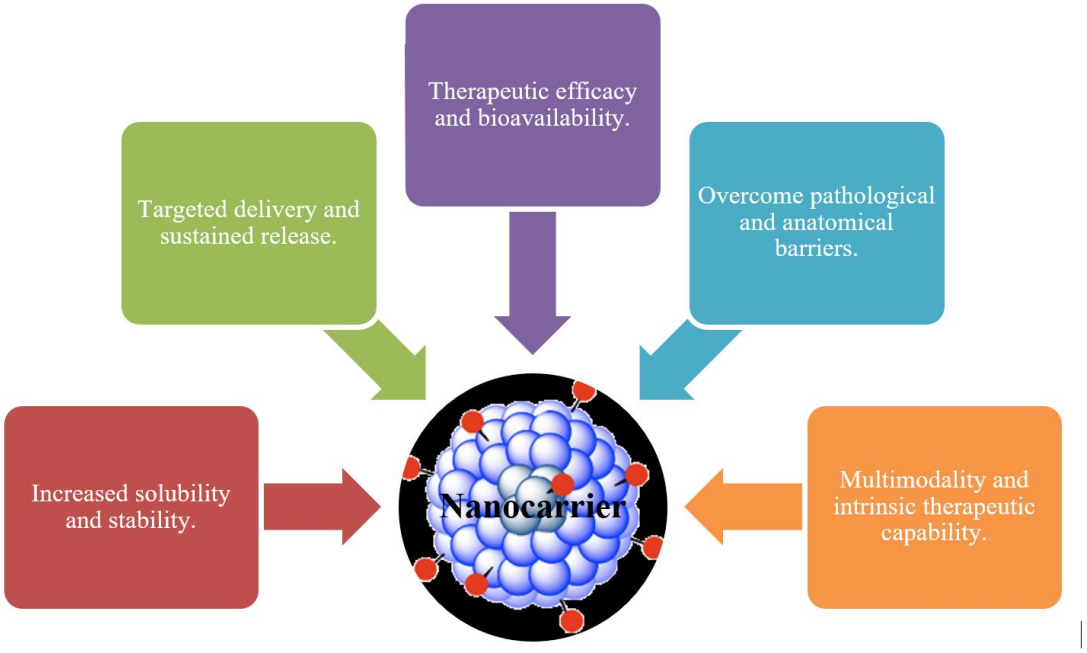

Figure 4. Key advantages of colon targeted NDDS

The industry of medicine has shifted due to the distinguished and distinct nature of nanoparticles. For instance, a study reported high susceptibility of pH, high efficiency of encapsulation along with improved bioavailability, safety and efficacy of doxorubicin. Study stated the utilization of strategy of grafting to load doxorubicin in a pH sensitive polymer (polyacrylic acid) with porous silica [42]. Another study reported the formulation of nanospheres using sodium alginate crosslinked to cysteamine via disulfide bond. The formulation improved the paclitaxel delivery to colon cancerous cells [43]. In a study, the infected CRC cells were targeted by the formulation of PEG (polyethylene glycol) modified nanoparticles having antigen carcinoembryonic in nature [44].

Liposome are nanosized carrier vesicles of phospholipid that are used in the delivery of the drug to colon. Improved half-life, biocompatibility and decreased recognition of macrophage was showed by liposomes of doxorubicin (PEGylated) [45]. Liposomes of 5 fluorouracil formulated with ligand (folic acid) when evaluated in vivo, showed improved cancer killing activity and better efficacy [46].

Therapies of tumors and cancers of colon are also being done with magnetic nanoparticles, which uses fluctuation of magnet to generate heating power. A stable, monodispersed with better cell internalization was achieved when magnetic nanoparticles of iron oxide was encapsulated with methyl dextran and epidermal growth factor [47]. Similarly, when Magnetospirillum gryphiswaldense (magneto tactic bacteria), when evaluated on HT-29 cultures of carcinoma cells of colon, no cytotoxicity with better uptake and anti-neoplastic action was observed [48].

Currently hybrid, inorganic, lipids and polymeric based nano systems are focused for colon based diseases. Some of the studies and their key findings are shown in table 2.

Nanocarrier	Study	Findings	Reference
Nanoparticles of silica	5-aminosalicylic acid nanoparticles were formulated with a prodrug approach and studied *in vitro*, using HEK and Caco-2 cells for ulcerative colitis.	Mitigated inflammation, enhanced tissue accumulation and reduced toxicity was observed.	[49]
Gold nanoparticles	Nanoparticles were injected intra-peritoneally in mice (*in vivo*) to study effect on colitis.	The gold nanoparticles showed anti-inflammatory and anti-oxidant action and lead to effective colon targeting.	[50]
Sustained action liposomes	Liposomes of oxaliptin and curcumin were formulated. For colorectal carcinoma *in vivo* studies, subcutaneous injection in tail vein was administered, Colo 205 and Lovo cells were used for the study.	They showed higher apoptotic action along with greater inhibition of growth.	[51]
	Liposomes of 5-aminosalicylic acid were formulated. For colitis study (*in vivo*), they were injected intraluminaly in rat while	The level of the drug was increased in the tissue with higher encapsulation efficiency.	[52]
Solid lipid nanoparticles	Nanoparticles of dexamethasone cholesteryl butyrate were orally administered and studied in BALB/c mice for *in vivo* studies and leukemic T cells for *in vitro* studies.	The formulation showed effective targeting to colitis infected area with lower adverse effects and high anti-inflammatory action.	[53]
	5-Fluorouracil based nanoparticles were prepared, optimized and studies *in vitro* using rat cecal.	The drug release was sustained after an initial burst release.	[54]
Nanoparticles of chitosan (pH sensitive)	Nanoparticles of curcumin were orally administered and studied in rat for *in vivo* studies.	They showed improved effects therapeutically and were accumulated in the colon.	[55]
Nanoparticles of polycaprolactone (time dependent release)	Nanoparticles of 5-aminosalicylic acid were orally administered and studied in mice for *in vivo* studies and in HEK and Caco-2 cells for *in vitro* studies.	The activity against colitis was enhanced therapeutically with selective and sustained release of the drug.	[56]
Nanoparticles of Eudragit RL 100 (mucoadhesive release)	Nanoparticles of clodronate were orally administered and studied in mice for *in vivo* studies and RAW 264 cells for *in vitro* studies.	The formulation showed improved anti-inflammatory activity, high delivery of macrophages with improved efficiency.	[57]

Table 2. Overview of colon targeted Novel drug delivery system.

5. Advances in Novel drug delivery system for colon targeted drug delivery

While designing novel drug delivery system for colon targeted drug delivery, there are many hurdles and barriers that needs to be handled for achieving improved efficiency. It should have therapeutic dose in specific amount, release the drug when required, distinguish between healthy and diseased tissue,

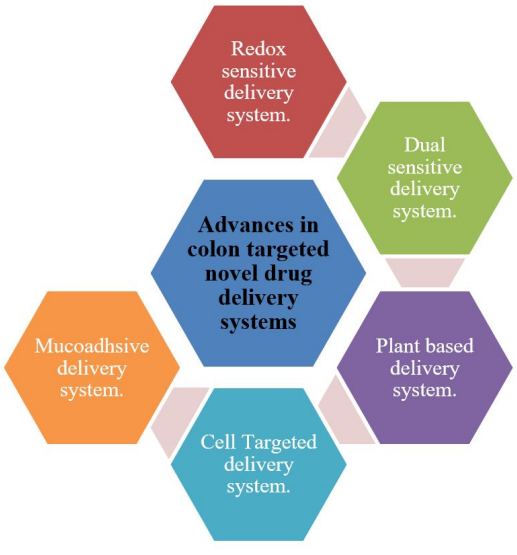

Figure 5. Advances in Colon targeting novel drug delivery system.

efficient colon targeting and should be able to cross the barriers in its pathway. Thus, to obtain a novel delivery system considering all the above factors, there is a need of some advances in the technology as shown in figure 5.

5.1 Redox responsive novel delivery systems

Formulations for delivery of drug which react to changes in potential of redox can be an effective option in treating ulcerative colitis and Colorectal cancer [58,59]. Ulcerative colitis is associated with the oxidative stress which leads to the excessive production of inflammatory Reactive Oxygen Species (ROS) [60]. Thus, delivery to the infected colon can be achieved by formulating novel systems that undergoes degradation by ROS. A study also reported suppression of colitis in mice when ROS scavengers (radicals of nitroxide) was incorporated in redox nanoparticles [61]. It was also stated that redox nanoparticles were able to suppress cancer of colon and were accumulated in the tissues of [60]. These systems appear as a novel platform for drug delivery to colon infected area, but it is also associated with instability and premature release of drug. This decreases the therapeutic efficiency of the drug delivery. Multiple responsive of stimuli can be used an approach to combat these issues.

5.2 Dual stimuli novel delivery systems

The key strategies used in delivery of drug to colon includes enzyme, pH and time dependent systems. But each of these systems is encountered with some limitations, that lead to poor efficiency of drug delivery. Systems dependent on pH are associated with premature drug release and absence of site specificity [62,63]. Salofalk, Salofac, Mesazal, Entocort, Clipper, Claversal, Asacol are some examples of the pH dependent marketed preparations for delivery of drug to colon [64,65]. Low efficiency of these preparations and inter/intra variability are some of the drawbacks of these formulations [66].

In case of time dependent systems, gastrointestinal transit time is responsible for the location of the release of the initial drug. It depends on the factors like variability among different individuals and presence of food. The release of the drug may be delayed in colon or the drug may be subjected to early release in the intestine [67,68].Time dependent systems showed sustained release of the drug after an initial burst release in the early region of gastrointestinal tract. This was due to the lack of pH dependent systems which leads to low efficiency and adverse effects of the system [69,70]. Enzymes present in colon degrades the natural polysaccharides, thus making them safe for utilization in the colon based delivery systems. But these natural agents are unable to provide controlled drug delivery and are hydrophilic in nature [71,72]. In addition, colonic microflora, transit time and pH are also influenced by variability of disease, which affects the efficiency of single stimuli novel delivery systems [73]. To overcome the drawbacks of single stimuli delivery systems, approach of dual stimuli novel delivery systems is in consideration such as pH/time and enzyme/pH [74,75].

Budesonide, Eudragit S 100 (pH sensitive polymer) and polyurethane (enzyme sensitive polymer) nanoparticles was utilized for formulating pH/ enzyme dual stimuli delivery systems to achieve sustained and effective colon targeting. Similarly, Cyclosporine, PLGA (time dependent polymer) and Eudragit FS30D (pH sensitive polymer) nanoparticles was utilized for formulating pH/time dual stimuli delivery systems. Both of these systems were evaluated for their tissue accumulation and drug delivery to colon in an animal model in which colitis was induced experimentally. The results showed that dual stimuli based systems were able to mitigate colitis, reduce adverse effects and were systemically absorbed in comparison to single stimuli based delivery systems. Thus, promising potential of nanotechnology when combined with dual stimuli delivery systems in treating colon diseases was demonstrated in in vivo and in vitro results.

5.3 Plant based nano systems

Synthetic nano based systems has already shown excellent potential in treatment of the diseases of colon. But are associated with the risk of toxic effects in the long-term utilization. Also, their production in large scale could be expensive for therapeutic trials and technically complicated [76]. Thus, to overcome the constraints of these synthetic nanoparticles, less costly and safe natural plants can be utilized to formulate nanoparticles. Low bioavailability, absorption and solubility are often associated when natural drug is administered directly [77].The therapeutic and physicochemical characteristics of a natural based source can be improved by the approach of nanotechnology, as it improves the solubility of poorly miscible drugs by reducing the particle size [78]. Proteins, lipids and miRNA are some of bioactive agents that are used for formulation of plant based nano systems.

In a reported study, nanoparticles of ginger extract were formulated with negative surface charge and 230 nm of particle size. These particles high concentration of bioactive ingredient, miRNAs, proteins and lipids. The results in the in vivo studies indicated that chronic colitis was avoided, healing of the intestine was improved, colitis was mitigated and no toxicity was observed [79]. Some other studies in mice like nanoparticles of broccoli extract and exosomes of grape extract also showed protective action against colitis [80,81].

High biocompatibility was showed by the nano-vectors derived from ginger when their lipids was reassembled to formulate nanoparticles. These nano-vectors were conjugated with folic acid and was loaded with doxorubicin. When evaluated in the in vivo studies in the mice, they were able to inhibit the spread of colon-26 tumors in comparison to free doxorubicin [82].Such responses recommend the use of plant based nano systems for the safe and efficient colon targeting.

5.4 Targeted novel delivery systems

The accumulation of the drug in the infected area of the colon is affected by both surface and size of the nanoparticle. The drug can be targeted to the specific area by interacting to the specific receptors or antigens that are overexpressed by immune and colonic cells during ulcerative colitis or colorectal cancer. Thus

for active targeting at the site of the disease, ligands like antibodies, mannose, lectin, hyaluronic acid and folic acid can be employed/conjugated with the surface of the nanocarriers [83]. These ligands make the nanocarriers attach to the specific adhesion molecule, protein, receptor at the site of the disease which enhances the internalization and adhesion of the nanoparticles to particular cells. This leads to reduction in adverse effects and increased efficacy due to the high accumulation of the drug at the site of target.

For the management of colorectal cancer, nanoparticles of PLGA loaded with apigenin and conjugated with aptamer was formulated [84]. The cell surface of colorectal cancer overexpresses a biomarker agent (adhesion cell of epithelial) which is targeted by the aptamer present on the nanoparticles surface. The results from the in vivo studies indicated enhanced efficacy, low cytotoxicity and high accumulation in the colon. Similarly, colitis mitigation was shown by tripeptides-based nanoparticles of PLGA and hyaluronic acid [85].

5.5 Mucoadhesive novel delivery systems

The mucus present in the colon system interact with the particles of nano carriers via hydrophobic binding which increase the retention and transit time of the nanoparticles [86].

The adhesion of the novel carriers to the colon membranes can be reduced or increased by modifying their surface [87]. Some studies reported the enhanced bioavailability of the drug in the small intestine to the adhesion to mucus [88-90].

Thus, it can be stated that mucoadhesive novel delivery systems can enhance the colon treatment by increasing the uptake and adhesion of the drug in the infected area [91,92].

However, this system is compromised by the adhesion of cationic nanoparticles to the proximal gastrointestinal region, before they reach the colon. Thus, to prevent this, the cationic nanocarriers are shielded with pH associated release, so that they are deshielded only in the region of the colon. Liposomes of budesonide rendered with cationic polyethyleneimine was formulated and was coated with Eudragit S100 (anionic) to prevent adhesion in proximal gastrointestinal region. The formulation on reaching the colon, was triggered by pH leading to the removal of the anionic layer and subsequent drug release. High tissue accumulation and drug release in the colon was observed by bioimaging and confocal analysis in the in vivo studies of mouse [93].

6. Other Recent Advancements in Colon-Drug delivery system

6.1 Solid dosage forms

Targeted delivery of the drugs is recently being done with capsules or film coated tablets. This type of delivery system is applicable to both low molecular synthetic drugs and macromolecules. The Eudragit L-100 coated tablets have been recently developed by Crowe et al. [94] to provide the anti-tumor necrosis factor. The tablet showed sustained release at 6 pH and in-vivo studies evaluation also indicated the sustained delivery of v65 to treat IBD topically. Consequently, ongoing efforts have been made to enhance the targeting through the multi-unit preparations based on various mechanisms related to the pH dependent coatings. Recently, Park et al. [95] developed a multi-unit tablet with bisacodyl by coating it with various pH based polymers like Eudragit L and time dependent polymers like Eudragit R. Sustained drug release was obtained within the colonic fluid whereas minimal release in the intestinal fluid was observed. Zein is the latent carrier responsible for the sustained release to deliver the hydrophobic drug molecules in the solid dispersion form to colon, as it shows resistance to the low pH surroundings [96]. A one-layer coated tablet has been developed recently by using Zein as biopolymer along with Kollicoat® MAE 100P which showed a high capacity to avoid the drug release in upper region of GIT for late release of drug to the colon [97]. Lately, a new coating innovation has been effectively sought to improve the viability of pH-delivery system. For instance, ColoPulse innovation is inventive pH responsive systems, which includes a super-disintegrant to the targeted site Gareb et al. [98] formulated the ileo-colonic tablet for the zero order targeted release of budesonide to treat IBD topically. The outcomes demonstrated that the medication discharge from the created tablet started in the ileum, and the discharge rate stayed consistent all through the whole colon. A further approach for site specific drug delivery is through preparation of capsules shells. These shells offer various benefits such as increased production with high speed based capsule filler, encapsulation of various drugs, and ultimately cost-reduction for research. Barbosa et al., [99] revealed a basic strategy for delivering enteric capsule shells with no extra covering advances. They arranged diverse enteric case shells to target the different area of the GI tract with the help of methacrylic acid derivatives (Eudragit® L100 and Eudragit® S100)/ cellulose subordinates (HPMC AS-LF and HP-55) along with acrylic polymers.

6.2 pH Dependent

The colon shows a moderately higher range of pH than upper GI tract, and this can be utilized as a technique for colonic drug delivery. Various polymers dependent on pH, for example, copolymers of methacrylic acid, hydroxypropyl methyl-cellulose phthalate (HPMCP) 50, cellulose acetic acid derivation

phthalates (CAP), and methyl methacrylate (e.g. Eudragit® L, Eudragit® S 100, Eudragit® P4135 F, and Eudragit® FS [100, 101]). Especially, Eudragit® polymers are the most broadly utilized copolymers for the colonic delivery of the drugs that offer muco-adhesiveness [102, 103]. For instance, patients with ulcerative colitis show increasingly acidic colonic pH contrasted with other people, prompting inadequate medication discharge from enteric coated frameworks [103]. Moreover, pH value of GI tract can be fundamentally changed by diet, infection state, water consumption, and microbial metabolism [104]. In the resulting human investigations, Ibekwe et al., [105] affirmed the absence of site-specific release of the drug with Eudragit® S coated tablets, due to different physiological elements including feed condition, gastrointestinal pH, and intestinal transit time. Another example of multi-unit system is Eudracol® that provides targeted delivery with slow and the uniform release of the medications [106].

6.3 Enzyme- based delivery system

Polysaccharides, for example, guar gum, gelatin, chitosan, and insulin have been utilized in colon-based medicate delivery system, since they can hold their integrity in the upper region of GI tract however are metabolized by colonic microflora to discharge drug [107]. Some new polysaccharides including arabinoxylans and agave fructans are additionally being investigated for colonic based delivery system [108, 109]. Additional advantage to this system includes large-scale production, cost reduction, lesser toxicity with higher biodegradability and biocompatibility. Song et al. [110] recently created a programmed drug release with magnetic resonance for orthotopic colon treatment of cancer. They choose Polyacrylic Acid (PAA) as a pH-responsive polymer and Chitosan (CS) as a chemical moiety degradable due to β-glycosidase present inside the colon.After administration through the oral route, CS and PAA may forestall premature medication discharge and lead to the enhanced concentration of the drug at the tumor sites.

6.4 Ligand based Delivery system

Ligand/receptor-framework utilizes different ligands (e.g., antibodies, folic acid, peptides, and hyaluronic acids) depending upon some of the specific receptors/ proteins at the targeted site. It alongside with pH-dependent systems, enhance stability in the GIT and provides site specificity. Harel et al. [111] formulated conjugated liposomes utilizing anti-transferrin receptor which showed enhanced internalization of cellular activity in comparison to unconjugated liposomes.. Furthermore, anti-transferrin receptor conjugated liposomes showed high distribution inside the inflamed mucosa instead of the normal mucosa bringing about more prominent aggregation at the inflammation site when analyzed to the normal mucosa. Also, Zhang et al. [112] developed a folate-altered self-micro emulsifying drug conveyance framework consisting of curcumin to improve its solubility for delivery to the colon. Their outcomes affirmed that this delivery system can reach to the colon proficiently and release the drug rapidly. Prajapati et al. [113] formulated hyaluronic acid-conjugated PEGylated multi-walled carbon nano tubes consisting gemcitabine (GEM/HA-PEG-MWCNTs) for direct targeting colon cancer. Hyaluronic acid was conjugated to the external layer of PEGylated Multi-Walled Carbon Nanotubes (MWCNTs). This plan demonstrated promising outcomes for viable colon malignant growth, focusing on improved proliferative action.

These days planning of dosage form is getting perplexing since there is a tremendous utilization of innovation in the measurement structures for controlling different angles. Recent models for the colon drug delivery system is shown in Table 3.

Technology	Dosage Form	Mechanism	Company name	Reference
MMXTM (Multimatrix technology)	Tablet	pH based and microbial activated	Cosmo pharmaceuticals	[114]
PHLORAL™	Tablet	pH and micro flora dependent	Intract Pharma	[114]
Diffucaps	Beads & Capsule	Multiparticulate system	Adare Pharmaceuticals	[115]
IPDAS (Intestinal protective drug absorption system)	Tablet	Multiparticulate system	Elan Corporation, Athlone	[115]
Peltab® (Pelletised tablet)	Tablet	Multiparticulate system	SPA corporation,	[115]
ETP Tablet (Enteric coated timed release press coated tablet)	Tablet	Time dependent system	Beacon Pharmaceuticals	[116,117]
Pulsincap®	Capsule	Time dependent system	R.P Scherer Corporation	[118]

Table 3. Advanced marketed preparations for colon based drug delivery.

7. Future Prospects

The structure of the nano-based systems has altogether propelled the future for colon treatment by improving the specific focusing of drugs to the site of action. Disease localization directs the requirement for intestinal drug delivery while the delivery of the drug ought to be limited to maintain a strategic distance from the undesirable side effects. This medication conveyance approach has been able to enhance efficacywith lower effective dose, decrease adverse events, and has permitted the utilization of novel mixes with drugs having poor physicochemical properties for oral conveyance. This has been accomplished through explicit biodistribution and aggregation in the intestinal areas. In the light of the outcomes to date, almost certainly, a mix of pharmaceutical techniques that have been examined in this review is required for ideal focusing to the colon. At last from a business advancement perspective, improvement of medication conveyance is required to permit productive and manufacturing at large scale. In interpreting these discoveries from laboratories to people, we have to decide how to adjust these details with the goal that they are fit for the administration by human. It is necessary to further explore the practicability of designing a delivery system which is feasible to humans.

8. Conclusion

Advanced colon based delivery of the drug is a fundamental system for treatment of colonic sicknesses, for example, colorectal malignant growths and IBD. It might offer numerous advantages over traditional therapy in terms of effectiveness, safety profile with patient compliance. Furthermore, colon-focused delivery systems are pertinent to improve the acids or additionally catalyst labile medications including micro and macromolecules.

Numerous obstacles must be conquered when building up an exceptionally efficient colon-specific delivery framework. The perfect colon-specific drug delivery system ought to have the option to beat the anatomical and physiological boundaries in GI tract area, recognize ailment target sites from tissues, target specific cells, and discharge on-request, specific portion of the therapeutic agent. Hence, novel delivery system has demonstrated extraordinary guarantee to defeat the previously mentioned difficulties, now and again alluded to as "enchantment shots". To accomplish effective and safe treatment for colon-specific infections, modifications in colon specific novel delivery system by adjusting their shape, size, surface ligands, and medication discharge conduct have been accounted for. These endeavors incorporate the revelation of the new biocompatible useful materials and the advancement of drug delivery devices.

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