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COLON TARGETED DRUG DELIVERY SYSTEM: DELIVERY APPROACHES, RECENT ADVANCEMENTS AND PATENTS

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ABSTRACT

To treat certain intestinal disorders such as Amebiosis, Colonic cancers, Crohn's diseases Ulcerative colitis, local colonic pathological treatment and systemic delivery peptide and protein drugs. Colon targeted drug delivery system is more acceptable. This article shows the delivery approaches for colon targeting such as Primary approaches include prodrugs, *pH* dependent system, time-dependent systems, and microbial drug delivery system have achieved limited success. Mechanical based colon targeted drug delivery approaches such as Osmotic controlled delivery of drugs, CODESTM and pressure controlled colonic delivery capsules are unique in terms of the specificity of the *in vivo* site and the feasibility of the manufacturing process and Novel approaches for colon targeted drug delivery such as Multiparticulate Drug Delivery System, Azo hydrogel, Nanoparticles, Liposomes and Microsphere can provide therapeutics benefits including patients compliance, reduce the doses of drug and also lower the cost of drug. This articles also shows recent advancements in various approaches for designing the colon targeted drug delivery system and also focused on patents that are accessible on present days in various colonic delivery.

KEYWORDS: Colon drug delivery system, Time Dependent, *pH* dependent, Polysaccharides based delivery, Novel Approaches.

INTRODUCTION

Targeted drug delivery to the colon is highly desirable for treating various bowel disorders such as Amebiosis, Crohn's Disease, Ulcerative Colitis, Colonic Cancer, Regional Colonic Pathology Treatment, and Systemic Protein and Peptide Delivery.[1,2] There are several advantages of dosage forms that supply drugs in the colon rather than the upper GIT. Oral delivery of drugs in the colon is useful in the treatment of colon diseases where elevated local concentration can be obtained for minimizing side effects. The colon attracts interest as a site where poorly absorbed drug molecule may have an enhanced bioavailability because of the colon.[3] The colon attracts interest as a site where there may be enhanced bioavailability of poorly absorbed drug molecule. There are different methods or strategies that can be used to target colon drugs, such as drug formulation, *pH*-sensitive polymers coating, biodegradable polymer coating, polysaccharide formulations design, timed-release systems, pressure-controlled drug delivery systems, osmotic pressure control systems.[4] The colon specific drug delivery system should be able to protect the drug on its way to the colon, i.e. there should be no drug release and absorption in both the stomach or small intestine, nor should the bioactive agent be destroyed at either dissolution site, but only released and absorbed once the scheme reaches the colon.[5] The most effective and favored route is the oral route, but other routes can be used for the Colon Targeted drug delivery process. Rectal administration provides the shortest route to treat the colon with medications. However, through rectal administration, it is difficult to enter the proximal portion of the colon. Rectal administration may also be awkward for patients, and compliance may be less than ideal.[6]

Drug selection criteria for CTDDS

The best candidates for CTDDS are medicines, like peptides, that show poor absorption of the Stomach or Intestine. Drug used to treat Inflammatory Bowel Disease, Vomiting, Ulcerative Colitis, and Colon Cancer are the perfect candidates for regional colon distribution. Table-1 summarizes the criteria for the selection of drugs for.[7-9]

Table 1: Selection criteria of Drug for colon targeted drug delivery.

Selection Criteria	Category	Drug
Drugs Poorly Absorbed From Upper GIT	Antianginal and antihypertensive drugs	Ibuprofen, Desmopressin, Cyclosporine
Drugs That Degrade In The Stomach and Small Intestine	Protein and peptides	5-Fluorouracil, Gonadorelin, Doxorubicin
Drugs used for local effects in colon against GIT diseases	Anti-inflammatory drugs	Nifedipine, Amylin, Metoprolol, Oxyprenolol

Drugs for colon cancer	Antineoplastic drugs	Pseudoephedrin, Epoetin
Drugs for targeting	Antiarthritic and Antiasthmatic drugs	Predinisolon, Somatropoin, Urotolitin, 5-Aminoslicylic Acid

Delivery approaches for Colon Targeted Drug Delivery System

Primary Approaches for CTDDS

***pH* control release**

The specific *pH* of human GIT is used in *pH*-controlled release systems by covering the dosage form with *pH*-dependent polymers that remain in the upper GIT as such and degrade in the large intestine where the *pH* is high, i.e. 7-8. This method can be used in any form of medication such as tablets, capsules, pellets etc. The active drug is covered against gastric fluid by coating the dosage forms with pH-sensitive polymers and a delayed release is also obtained. By collecting total polymer information and its solubility at various pH levels, delivery systems are designed to guide the drug to the desired location. The most widely used polymers for colonic drug delivery are methacrylic acid and methyl methacrylate. On the in vitro assessment of Eudragit S and Eudragit FS, the latter was found to be more suitable for the delivery of ileocolonic drugs.[10-13]

Delayed (Time controlled release system) release drug delivery System

Due to potentially large variations of gastric emptying time of dosage forms in humans, the arrival time of colon dosage forms cannot be estimated correctly in this methods, leading in bad colonial accessibility.[14] The strategy in designing time-released systems is to resist the acidic environment of the stomach and to undergo a lag time of the predetermined period after which the release of the drug takes place. In this case, the lag time required to transit from mouth to colon is usually considered sufficient for a lag time of 5 hours, since the small intestine is about 3-4 hours, which is relatively long.[15]

Microbial triggered system

The microbial activated delivery system is more convenient and extremely site-specific strategy than any targeting system for targeting the drug to the colon. In this system the drug is released, when the bacteria of the colonic microflora degrade the polysaccharides.[16] There is a microflora of less than 10^3 - 10^4 CFU/ml in the bottom portion of GIT, i.e. the stomach and duodenum. On the other hand, the microflora of Colon is 10^{11}-10^{12} CFU/ml, composed primarily of anaerobic bacteria. E.g. Bactericides, Bifid bacteria, Eubacteria, Clostridia Enterococci, Enterobacteria, etc. Vast numbers of enzymes such as glucuronidase,

xylosidase, arabinosidase, galactosidase, nitroreductase, azoreductase, deaminase, and urea dehydroxylase are produced by microflora. Because these biodegradable enzymes are present only in the colon, the use of bacterial degradable polymers for colon-specific drug delivery appears to be a more site-specific enzyme.[17]

Pro-drug approach for colon

It is created by Chemical modification of biologically active compounds that releases the active compound in vivo through enzymatic or chemical processes.[18] Pro-drug is the primary strategy of the microbial activated drug delivery system in which the microflora present in the gut triggers the drug release from the formulation.[19] In particular, as a colon drug carrier it is hydrophilic and bulky, a pro-drug is effective in reducing absorption from the upper GI tract and once in the colon it is converted into a more lipophilic drug molecule which is then available for absorption.[13] A clinical study has shown clear proof that β-cyclodextrins are poorly digested in the small intestine but are degraded by colonic microflora almost entirely.[20] Fig. 1 show the Pro-drug delivery approach.

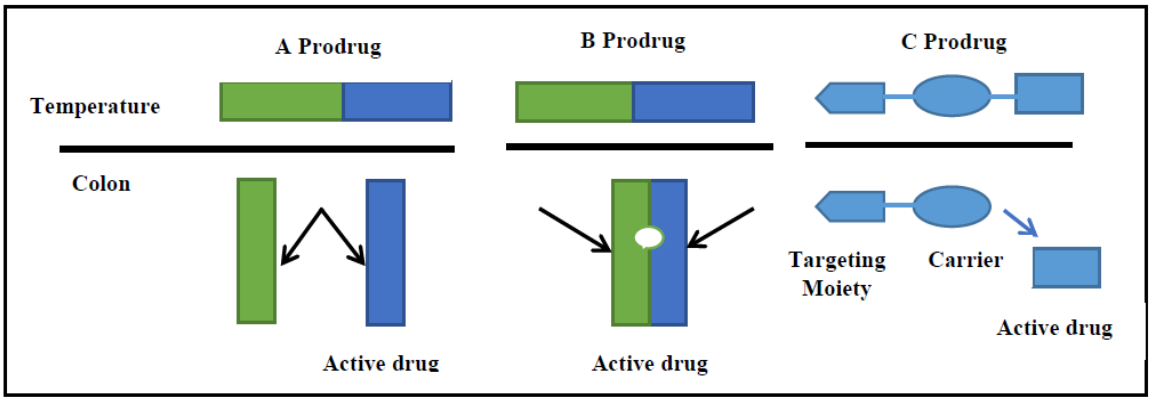

Fig 1: Pro-drug approach.

Polysaccharide Based delivery system

By compressing the combination of active drugs, a degradable combination of active drugs, a degradable polymer, and additives, the drug is inserted into the biodegradable polymer matrix core.[21] Work on many natural polysaccharides, such as chondroitin sulfate, pectin, dextran and, more specifically, guar gum, etc., has begun on their ability to innovate colon-specific drug delivery. These are caused to break down into easy saccharides by the colonic microorganisms.[22] They can be easily altered chemically, biochemically, and are extremely stable, safe hydrophilic, non-toxic, and biodegradable. In addition, the use of naturally occurring polysaccharides attracts a lot of interest for colon-targeting drugs because these

polymers are abundantly found, widely available, inexpensive and usable in a multitude of structures with different properties.[23]

Mechanically Based Approaches for CTDDS

Pressure Controlled drug-delivery system

Increased pressure in the colon as compared to the small intestine Takaya et al. developed pressure controlled colon- delivery capsules prepared using ethyl cellulose that is insoluble in water due to peristalsis.[24] Peristaltic movement leads the large intestine luminal stress to raise more than the tiny intestine because its contents are more viscous due to water reabsorption. Several trials were conducted to use colonic luminal stress to create colon-specific drug delivery systems.[25] These gelatin capsules are covered with a water-insoluble polymer such as ethyl cellulose on the inside of the capsule, together with suppository base dissolves at body temperature the water from the absorbed intestinal contents resulting in enhanced viscosity resulting in enhanced stress in the capsule expelling the medicine into the colon.[26]

Pulsatile colon targeted drug delivery

Pulsin Cap System

The pulsin capsule regulates the drug release. Swellable hydrogels are used to seal the contents of the drug. The capsule swells when it comes into touch with the dissolution fluid and after a delay, the plug is pushed out of the capsule and the drug is released.[27] Hydrogel plug are used with polymers such as various grades of hydroxyl propyl methylcellulose (HPMC), polymathic methacrylate and polyvinyl acetate. The log time is regulated by the capsule body's length and intersection point.[19] Fig. 2 shows Pulsin Cap system.

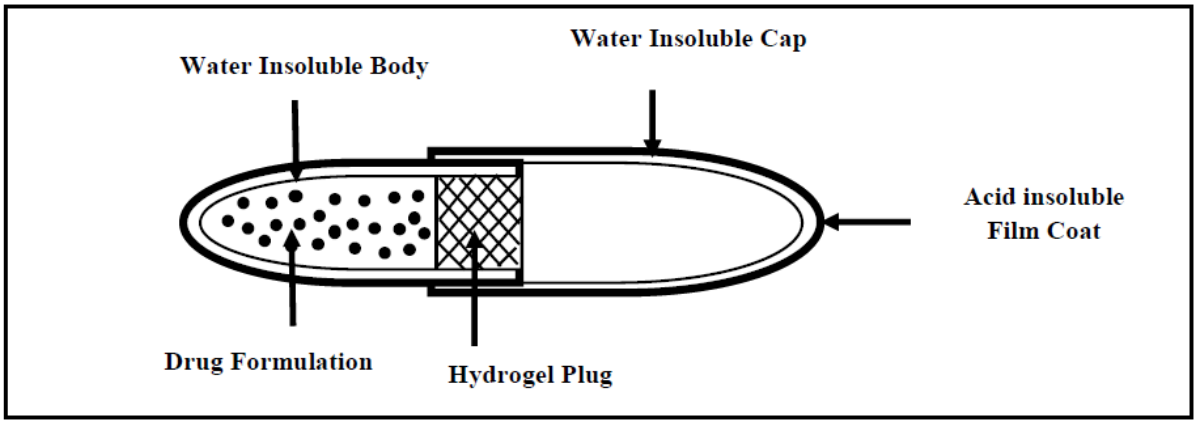

Fig 2: Pulsin Cap system.

Port system

Port System was established in the therapeutic system research laboratory Ann Arbor, Michigan, USA, and consisted of a capsule covered with a semi-permeable membrane, inside the capsule there was an insoluble plug consisting of an osmotic active agent and drug formulation.[28] The semi-permeable membrane permitted the entry of water when this capsule came into contact with the dissolution fluid, which caused the stress to grow and the insoluble plug to expel after a lag moment.[29] This system prevents second-time dosage, which was useful during the day for college kids.[30] Coating thickness controls the lag time. In the lag moment of human in-vitro and in-vivo studies, the scheme showed excellent correction.[31] Fig. 3 show the Plan of Port System delivery approach.

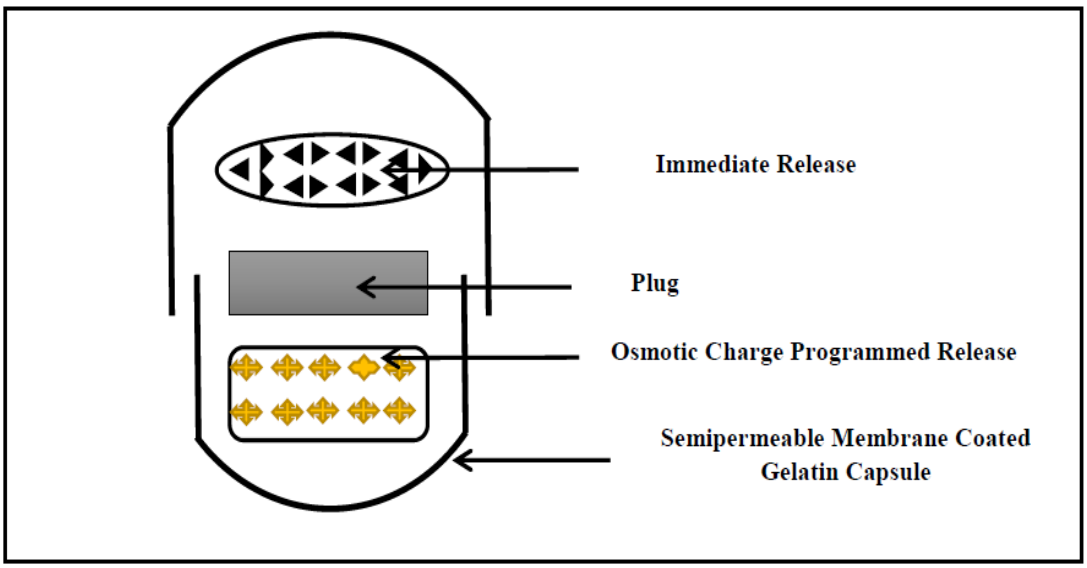

Fig 3: Plan of Port System.

CODES Technology

In this system, the *pH* and microbially activated method are used at the required place to control the release of the drug.[32] It was created using a distinctive lactulose mechanism that acts as a trigger for the site-specific discharge of drugs in the colon.[33] It comprises of three-layer core tablets covered with polymer coatings.

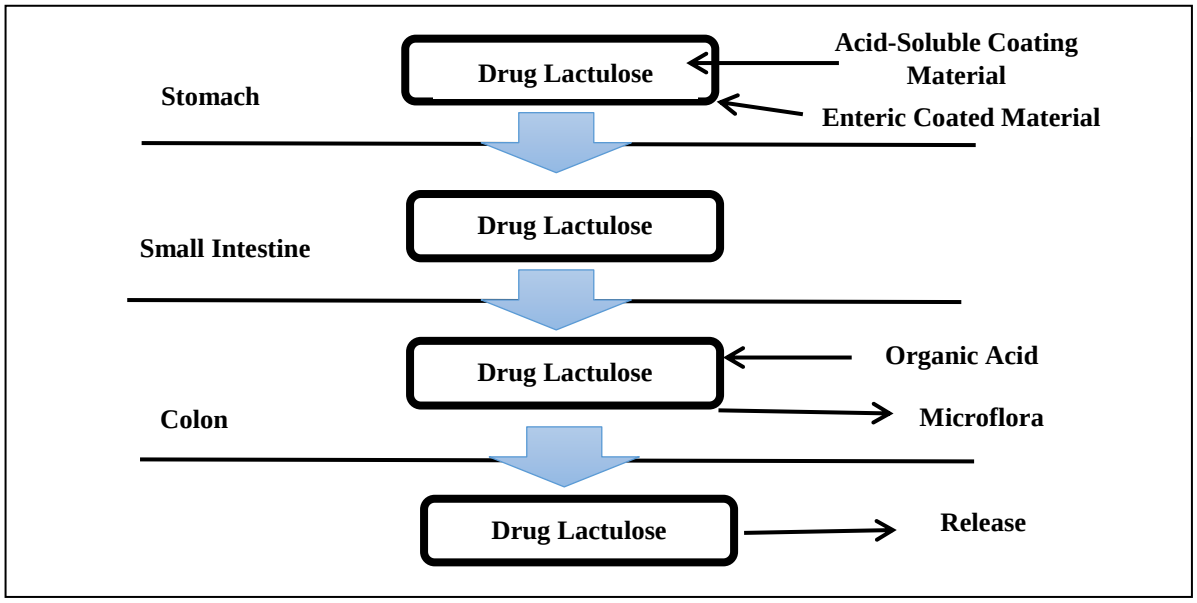

Fig 4: CODES System.

The first coating is an acid-soluble polymer and the exterior layer is enteric with an HPMC barrier layer between them to avoid any possible contact between the opposing polymers.[34] The other polysaccharide used in the core along with the drug. Tablets are mannitol, maltose, etc. The bacteria present in the colon are liable for the degradation of polysaccharides produced from the key tablet.[35] Fig. 4 show the CODES System delivery approach**.**

Osmotic Controlled Drug Delivery (OROS-CT)

The OROS-CT may be a single osmotic agent or may consist of up to five to six push-pull osmotic units filled in a tough gelatin capsule.[35] The gelatin capsule dissolves after contact with GI liquids and the enteric coating avoids the entry of liquids into the system.[36] The osmotic pumping action results when the coating dissolves in the small intestine's elevated pH setting ($pH>7$) and the drug is supplied from the orifice at a speed regulated by the speed of water transport across the membrane.[37] Fig. 5 show the OROS-CT delivery approach**.**

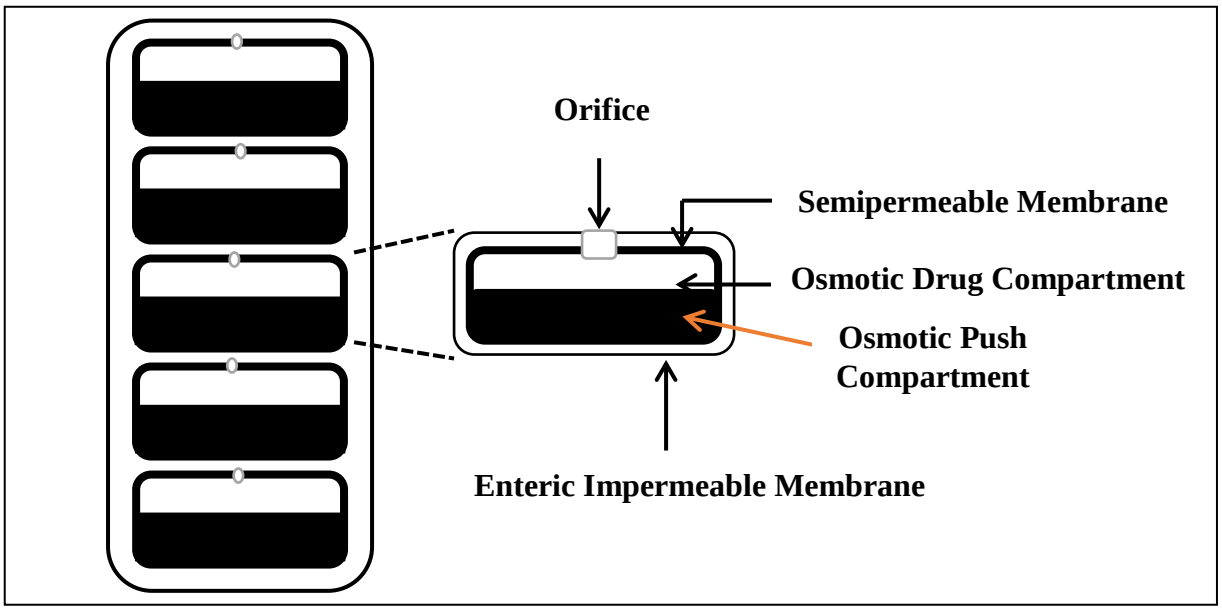

Fig 5: OROS-CT.

Novel Approaches

Multiparticulate Drug Delivery System

Multiparticulate Drug Delivery Systems are predominantly Oral Dosage Forms composed of a multitude of small discrete units, each with certain required features.[38] The multiple benefits of this scheme include increased bioavailability, reduced risk of local irritation, reduced risk of systemic toxicity. The different multiparticulate methods are pellets, micro particles, granules and Nano-particles.[39] To prescribe or recommend full dosage, these subunits are condensed into a tablet or filled into a sachet or encapsulated. They can protect the drugs against chemical and enzymatic degradation in GIT leading to increased stability and absorption through the intestinal epithelium.[40]

Azo hydrogel

The colon specificity is produced by the pH-sensitive monomers and azo cross-linking agents in the hydrogel. These hydrogels swell as the pH increases as they pass through GIT. This swelling of hydrogels breaks down the hydrogel network interconnections, allowing the hydrogel to release drugs.[41]

Nanoparticles for colon targeted drug delivery

Nanoparticles are now a new area for the delivery of colon-specific drugs. These are new approaches that are used to target drugs. These are thin, around 100 nm-sized colloidal particles made of biodegradable and non-biodegradable polymers. The moiety of the drug

may be dissolved, trapped or encapsulated in the matrix of nanoparticles.[42] Nanoparticles include various types such as metallic Nanoparticles, Carbon Nano Tubes, biodegradable polymers, and dendrimers that are used to facilitate colon drug delivery.[43] Specific surface chemistry and size of Nanoparticles make them active in targeted delivery of colon drugs, while improving permeability enables them to insert and penetrate inflammatory sites through the intestinal wall, which will ultimately help to better absorb tissue. Particulate residential time increases with size reduction, particles below the 10μm size range accumulate in the inflamed area, but the size range of nanoparticles minimizes drug clearance.[44] Nanoparticles also have flexible physicochemical properties that can be applied effectively to improve the concentration of drugs in the colon and to reduce systemic side effects.[45]

Microspheres for colon targeted drug delivery

Microspheres are now being used for protein and peptide delivery for days. They provide stability for compounds that are prone to *in vivo* degradation. The microspheres shield the drug from the acidic stomach environment and direct the drug to the desired site, as well as enhance drug absorption from the Para cellular path.[46] Biodegradable polymers or protein-based microspheres with free-flowing properties and 5-200 nm particle size have many advantages over traditional drug delivery systems. Where the environmental factors are highly variable from patient to patient and in different diseases, they can provide localized delivery, sustained delivery, and stabilization of the sensitive drug.[47]

Liposome for colon targeted drug delivery

Liposomes are Nano size phospholipid bilayer vesicles used for selective delivery of colon drugs.[43] PEGylated liposomes of doxirubicin showed decreased macrophage recognition, improved biocompatibility, improved half-life.[48] 5-Fluorouracil loaded folic acid liposomes as ligand were prepared to target colon cells, and it was studied *in vivo* efficacy where 5-Fluorouracil liposomes showed better involvement in cancer cell killing.[49] On Caco 2 colon cancerous cells, doxorubicin-loaded liposomes were produced and tested, showed better circulation time, better internalization of the drug, and much less cytototoxicity.[50]

Recent advancements in Colon Targeted Drug Delivery System

Ligand Mediated Drug Delivery System

Ligand mediated systems have been explored to improve the target specificity through the interaction of targeting ligands of the carrier surface with similar receptors expressed at the

disease locations to more successful local treatment of colonic diseases with reduced toxic side effects. The mechanism controlled by Ligand can be designed based on the functional expression profiles for such receptors/proteins in the target cells/organs, using specific ligands (e.g. antibodies, peptides, folic acids, hyaluronic acids). In addition, it can also be combined to improve its GI stability and site specificity with pH-reliant systems if necessary.[51,52] There are some ligands which are used for Colon dug delivery. One of the ligand is antibodies which are used in colon targeted drug delivery. Harel *et al*. Prepared anti-transferrin receptor antibody –conjugated liposome indicates greater cell internalization of the conjugated liposomes compared to non-conjugated liposomes. Furthermore, liposomes combined by anti-transferrin receptor showed preferential distribution in inflamed mucosa instead of normal mucus, causing greater (more than 4-fold higher) accumulation at the site of an inflammation than usual mucosa.[53] Another ligand is Folic acid, a water-soluble supplement, a tumor targeted ligand and in certain forms of cancer, the folat receptor is overexpressed.[54] Xiong *et al*. reported that folic acid-conjugated liposomes allowed folate-mediated medicines to boost the cancer activity of daunorubicin.[55] Peptide is another ligand mediated drug delivery system which are also used as a colon specific drug delivery system. As a possible ligand for selective drug delivery, Peptide receives considerable interest. Peptides have many advantages such as biocompatibility, performance, chemical diversity and stimuli. Moreover, peptide ligands have a much greater relation and specificity than small molecular ligands because of the large binding interfaces to receptors.[56,57] Ren *et al*. research the use for the colon-specific delivery of anticancer medications of synthesized 12-residues peptide (TWYKIAFQRNRK, TK peptide). TK has a high integrin affinity of α6β1, an integrin subtype that is upregulated in cells of human colon cancer. TK peptide was then joined as a guided ligand with PEG-PLA micelles loaded with doxorubicin. This TK-spoused micelle had substantially greater cytotoxicity and penetrated tumor spheros more effectively, suggesting that TK peptide was a promising ligand to target the colon.[58]

Drug Delivery System Via Magnetic Drive

Different methods for guided and targeted drug delivery originated from magnetic microcarriers, including magnetic microspheres, magnetic nanoparticles, magnetic liposomes and magnetic emulsions. Grifantini *et al.* developed two new magnetic characteristics magnetically adaptable magnetic drug delivery systems for improving the targeted treatment of colorectal cancer through mAb198.3 (a monoclonal antibody unique to FAT1), in which mAb198.3 was directly connected to super-paramagnetic nanoparticles or inserted into

human erythrocyte-based magnetized carriers in order to enhance targeted treatment of colorectal cancer by mAb198.3. They found that both systems target colon cells and prevent growth of cancer at slightly lower doses. They found that both systems are extremely successful. This study showed the capacity of magnetically controlled drug delivery systems to increase the bioavailability of the anti-FAT mAb198.3 targets to open up a new route for colon-based drug delivery.[59] The efficacy of hydrocortisone with a magnetic belt on rats was further improved in a previous report. This nanodevice consisted of magnetic mesoporous, hydrocortisone coated silica microparticles. Using a dense azo derivative and urea moeties, the exterior surface of the drug-loaded nanoparticles was functionalized. However, in the presence of sodium di thionite, the nanodevices remained confined to neutral pHs, since it decreased the azo bonds in the capping joint.[60] Kono *et al.* recently developed magnetically guided cell delivery systems through the incorporation into raw 264 murine macrophage-like cells of superparamagnetic iron oxide nanoparticles (SPIONs) and plasmid-DNA (pDNA). They also shown that this magnetic cell delivery system can boost colonic macrophages delivery in mice.[61]

Nano Drug Delivery System for Colon Targeted

A higher performance, colon targeted Nano-drug delivery system must address various challenges. The ideal method would resolve biological hurdles, target the colon, separate diseased from healthy tissue, and free the dose of therapeutic agents on request. As a result, innovative innovation and successful oral Nano Drug Delivery System (NDDS) aimed at colon has been made to overcome the aforementioned challenges and improve the loaded drug therapeutic profile significantly. Development in colon-specific NDDS. Recent studies have proposed novel NDDS systems for dual sensitive, redox-sensitive, plant-sustaining, mucus-adhesive and penetrating systems, for cell-compared and nanoparticle systems to address barriers to the delivery of colon-specific drugs in IBD and CRC treatments.[62] Mucoadhesive properties allow formulations to increase transit time by adhering to layers of mucosa lining the GI tract.[63] Mucous binding NDDS may also interact with charged carrier particles and hold them at mucosal barrier via hydrophobic interactions or charged groups of mucin proteins.[64,65] Several studies have shown that cationic NDDS can bind to mucus in the gut and thus can enhance bioavailability of systemic medicines.[66-69]

Drug supply formulations leading to redox potential changes may become a promising technique for CRC and UC care.[70,71] UC has been associated with over-production by

inflammatory cells of reactive oxygen (ROS) species in response to oxidative stress.[72] Thus, NDDS, which is impaired by ROS, may release drugs to inflamed colon tissues in particular. Based on this definition, nitroxide radicals have been documented to be suppressed by redox NPs (RNPs), which have ROS scavenger in their center.[73] The same group recently found that RNPs actually accumulated in cancer tissues and that colitis-associated colon cancer is substantially suppressed.[71] Although ROS-responsive Nano-living systems are a new approach to target inflamed tissues in UC in particular.[74,75]

In the treatment of colon-specific diseases, synthetic NDDS has demonstrated great potential. Their long-term use can, however, carry a risk of in vivo toxicity. Second, large-scale manufacturing can be costly and technologically difficult for clinical applications.[76] On the contrary, the use of natural sources of NPs is considered healthy and inexpensive and can surpass synthetic NP limits. Due to low solubility, absorption and bioavailability, direct administration of a natural product is often restricted.[77] Reducing particulate size is one of the most effective and realistic approaches for increasing the solubility of the poor water-soluble drug.[78] It has been reported recently that ginger, grapefruit, carrots and tomatoes related plant NPs can be isolated in eco-friendly technique.[79] Plant-based edible NPs with bioactive agents including miRNA, lipid and protein can serve as natural therapies for a variety of diseases. Recently, in order to prevent and treat IBD and CRC, ginger-derived edible NPs (GDNPs) have been introduced. In animal models the GDNPs were not harmful. The study showed GDNPs reducing colitis, improving bowel healing and avoiding CRC and chronic colitis.[80]

Patents based on Colon Targeted Drug Delivery System

Table 2: Patent on Colon Targeted Drug Delivery System.

Inventor Name and Year	Patent title	Patents No.	Ref.
Beckert T et al. (2003)	Multilayer Pharmaceutical product for release in the colon.	US6632454B2	[81]
E. Fattal et al. (2005)	Galenic formulation for colon targeted delivery of active principles.	US20050249716A1	[82]
Percel et al. (2006)	Timed Pulsatile Drug Delivery Systems.	US20010046964A1	[83]
AW Basit and VC Ibekwe (2007)	Colonic Drug Delivery Formulation.	US 20070243253A1	[84]
S. Bourgeois et al. (2009)	Galenic Pectinate Formulation for Colon-Targeted Delivery of Antibiotic-Inactivating Enzymes And Method of	US7485294B2	[85]

	use Thereof.		
H. Huguet et al. (2011)	Site-specific intestinal delivery of adsorbents, alone or in combination with degrading molecules.	US8048413B2	[86]
RM Navari et al. (2011)	Cathepsin E as a marker of colon cancer.	US7892750B1	[87]
Huguet et al. (2012)	Colonic delivery of adsorbents.	US8106000B2	[88]
S Sudarsky et al. (2012)	System and method for colon unfolding via skeletal subspace deformation.	US8300047B2	[89]
JM Abraham et al. (2013)	Small Peptides Specifically Bind to Colorectal Cancers.	US8435490B2	[90]
JR Szewczyk (2013)	Composition and Method for Treatment of Diabetes.	US8470885B2	[91]
I Coulter (2013)	Pharmaceutical Cyclosporin Compositions.	US8535713B2	[92]
GP Dittmar et al. (2013)	Pharmaceutical dosage form with multiple coatings for reduced impact of coating fractures.	US8580302B2	[93]
T Mickle et al. (2013)	Active agent delivery systems and methods for protecting and administering active agents.	US8394813B2	[94]
GC Viscomi et al. (2013)	Gastroresistant Pharmaceutical Formulations Containing Rifaximin.	US8568782B2	[95]
MA Imran (2013)	Optical Capsule And Spectroscopic Method For Treating Or Diagnosing The Intestinal Tract.	US8360976B2	[96]
R Kamaguchi (2014)	Capsule Which Disintegrates Specifically in the Large Intestine.	US8747893B2	[97]
RF Harty (2014)	Compositions and methods of treatment for inflammatory diseases	US8629127B2	[98]
Szewczyk JR (2014)	Composition and method for treatment of diabetes.	US8680085B2	[99]
GM Venkatesh (2015)	Timed, Pulsatile Release Systems.	US9161918B2	[100]
Haeusler et al. (2015)	Water insoluble polymer: indigestible water-soluble polysaccharide film coatings for colon targeting.	US9107819B2	[101]
Percel et al. (2016)	Timed, Sustained Release Systems for Propranolol	US9358214B2	[102]
EA Mash Jr et al. (2016)	Method and Compositions for Targeted Drug Delivery to the Lower GI Tract.	US9415110B1	[103]
Dohil et al. (2017)	Topical corticosteroids for the treatment of inflammatory diseases of the gastrointestinal tract.	US9782347B2	[104]
Varum et al. (2017)	Delayed release drug formulation.	US20170035698A1	[105]
Stremmel W (2017)	Bacterial phospholipase inhibitors as modulator of colonic bacterial flora.	US20170173165A1	[106]

Varum et al. (2017)	Delayed release drug formulation.	US9814681B2	[107]
Mishra et al. (2017)	Intraluminal pressure detection for diverticular disease.	US9534977B2	[108]
AW Basit, and VC Ibekwe (2018)	Colonic Drug Delivery Formulation.	US9993435B2	[109]
TM Fahmy et al. (2018)	Polymeric bile acid nanocompositions targeting the pancreas and colon.	US20180243226A1	[110]

CONCLUSION

Colon targeted drug delivery system is essential approaches for more effective local treatments of colon diseases such as Ulcerative colitis, IBD and colorectal cancer. In terms of health, effectiveness, and patient compliance, it can deliver several benefits over traditional dosage types. Colon targeted drug delivery system offers important clinical benefits for patients in terms of both regional and comprehensive treatment. The main advantage of the colon drug delivery system is long transit time, near to neutral *pH*, reduced enzymatic activity, improved absorption enhancers responsiveness and providing a friendly environment for protein and peptide drugs that reduces adverse effects in the treatment of colonic diseases, site-specific release for the treatment of colonic cancer, helminthiasis, etc., minimizing the extensive first-pass metabolism of steroids and delaying the absorption of drugs for the treatment of Rheumatoid Arthritis, Angina and Nocturnal Arthritis. In this review articles, several formulation approaches design for the effective colon targeted drug delivery system were discus and all these formulation approaches showed their own advantages and limitations. In addition, Nano/micro-particles hold great potential for enhancing drug targeting as well as drug uptake. To achieve safe and effective therapy of colon-specific diseases, advances in colon-targeted Nano drug delivery system by modulating their size, shape, surface ligands, and drug release behavior have been reported.

ACKNOWLEDGEMENT: NA.

ABBREVIATION

GIT: Gastrointestinal Tract; **CTDDS**: Colon Targeted Drug Delivery System; **CFU**: colony-forming unit; **HPMC**: Hydroxyl Propyl Methylcellulose.

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