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Recent Advancement in Colon-Targeted Drug Delivery

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Abstract:

In the past two decades, colon-targeted drug delivery has become more significant due to its ability to deliver therapeutic proteins, peptides, and medicines for the treatment of numerous colonic disorders. Traditional methods for colon-targeted administration, including Prodrugs, pH, time-dependent, and microflora-triggered systems, have shown varying degrees of effectiveness in the past. The medicine must be shielded from absorption and/or the environment of the colon for effective colon-targeted drug delivery. Abruptly released into the colon after passing through the upper gastrointestinal tract Into the various therapeutic demands, ongoing efforts have been made to build colon-targeted drug delivery systems with increased site specificity and adaptable drug release kinetics. Recent years have seen the development of several new systems for colon-targeted drug delivery, including pressure-dependent systems, microscopic sponges, pectin and galactomannan coating, microbially triggered osmotic systems, lectins and neoglyconjugated, among others. These systems are said to have better in-vivo site specificity and design rationale than earlier ones. This item of review provides a summary of different strategies for colonic-targeted drug administration.

Keyword: Colon-targeted drug delivery, anatomy, Ph dependent, patent, Approaches, Microflora.

Introduction:

Due to its potential to enhance the treatment of local disorders affecting the colon while limiting systemic side effects, colon-targeted medication delivery has attracted a lot of attention in recent years [1]. Solid oral dosage forms have historically been created to release their drug content in the gastrointestinal tract's upper parts, typically more conducive to drug absorption and breakdown. Controlling the rate and/or site of medication release from oral formulations has received more attention recently to increase patient compliance and therapeutic effectiveness [2]. Colonic delivery is the term used to describe the targeted administration of medications into the lower GI tract, especially the large intestine (i.e. colon) [3]. Oral consumption is the easiest and most crucial way to give medications for a systemic impact. Oral Drug delivery system. Makeup is about half of the drug delivery systems on the market, and these systems have more benefits due to patient acceptance and ease of administration [4]. Drugs that are polar and/or vulnerable to chemical and enzymatic reactions can be delivered using formulas for colonic administration. Therapeutic proteins and peptides in particular are appropriate for delivery via intestinal absorption due to upper GIT degradation. Proteins and peptides can be given regularly by intestinal absorption, including insulin, calcitonin, and vasopressin. Novel peptides that help treat IBD and GI infections, respectively, include cytokine inhibitors and antibiotics [5]. Formulas for colonic administration can be used to administer medicines that are polar and/or susceptible to enzymatic and chemical interactions. Due to the upper GIT's ability to degrade therapeutic proteins and peptides, intestinal absorption is the best method for delivering them. Insulin, calcitonin, and vasopressin are a few examples of proteins and peptides that can be administered regularly by intestinal absorption. Cytokine inhibitors and antibiotics are two novel peptides that can be used to treat IBD and GI infections, respectively [6]. Colon-focused drug delivery

systems are made to release a medicine only when it is required to respond to the colonic environment, preventing an untimely release of the drug into the upper GI tract. Therefore, it is crucial to consider the colon's physiological characteristics and the milieu around the disease site(s) for the successful development of colon-targeted drug delivery systems [7].

Need for the development of colon-targeted drug delivery:

The colon is a perfect location for the administration of therapeutic medicines. The colon's regional illnesses. The benefit of local therapy is that it only needs lesser doses of the medication. Reduces the frequency of doses. The cheaper price of costly medications [8].

Anatomy Of the colon:

From 40 to 400 different kinds of bacteria can be found in the intestinal lumen, which supports a wide range of them. The colon has a significantly higher bacterial count than the stomach, with 1011–1012 CFU/mL.where the bacterial density is approximately 103 CFU/mL in the GIT's first parts. In comparison to those found in the small intestine, the peptidases produced by this flora are very different. These peptidases can either be extracellular or cell-bound and are all capable of breaking down proteins. The remaining pancreatic peptidase activity can also be seen in the colon's contents. Low quantities of hydrolytic enzymes are present in the intestinal cells, which are less developed. According to research by Bai et al, the least active proteolytic membranes are those in the caecum. The colon is chosen for targeting proteins and peptides for a variety of reasons, but it also poses several risks and challenges to overcome [9].

Under a light microscope, the colon can be observed to have several concentric layers (histology). Columnar mucosa, foundation membrane, and lamina come first in the lumen. Serosa, muscularis propria, muscularis mucosae, sub mucosa, inner circular layer, outer incomplete longitudinal layer (taenia coli), and muscularis propria. The colon features rather flat undulating folds as opposed to the ileum, which contains florid villi [10].

Four sections of the colon—the ascending, transverse, descending, and sigmoid—can be distinguished along its average length of 150 cm. [11]

1] Ascending colon:

The ascending colon, a retroperitoneal structure that rises superiorly from the cecum, is the first part of the colon. It twists 90 degrees and moves horizontally when it encounters the right lobe of the liver. The transverse colon begins at the right colic flexure, also known as the hepatic flexure.

2] Transverse colon:

The transverse colon extends past the right colic flexure and continues to the spleen, where it bends inferiorly and twists another 90 degrees. Left colic flexure refers to this turn (or splenic flexure). In this instance, the phrenicocolic ligament connects the colon to the diaphragm.

3] Descending colon:

The descending colon, which follows the left colic flexure and proceeds inferiorly into the pelvic, is known as this. Most people have retroperitoneal locations, however, in this case, it is anterior to the left kidney and crosses its lateral border.

4] Sigmoid Colon:

In the left lower quadrant of the abdomen, from the level of the S3 vertebra to the left iliac fossa, is the 40cm-long sigmoid colon. Because of this travel, the sigmoid colon has its distinctive "S" shape. [11]

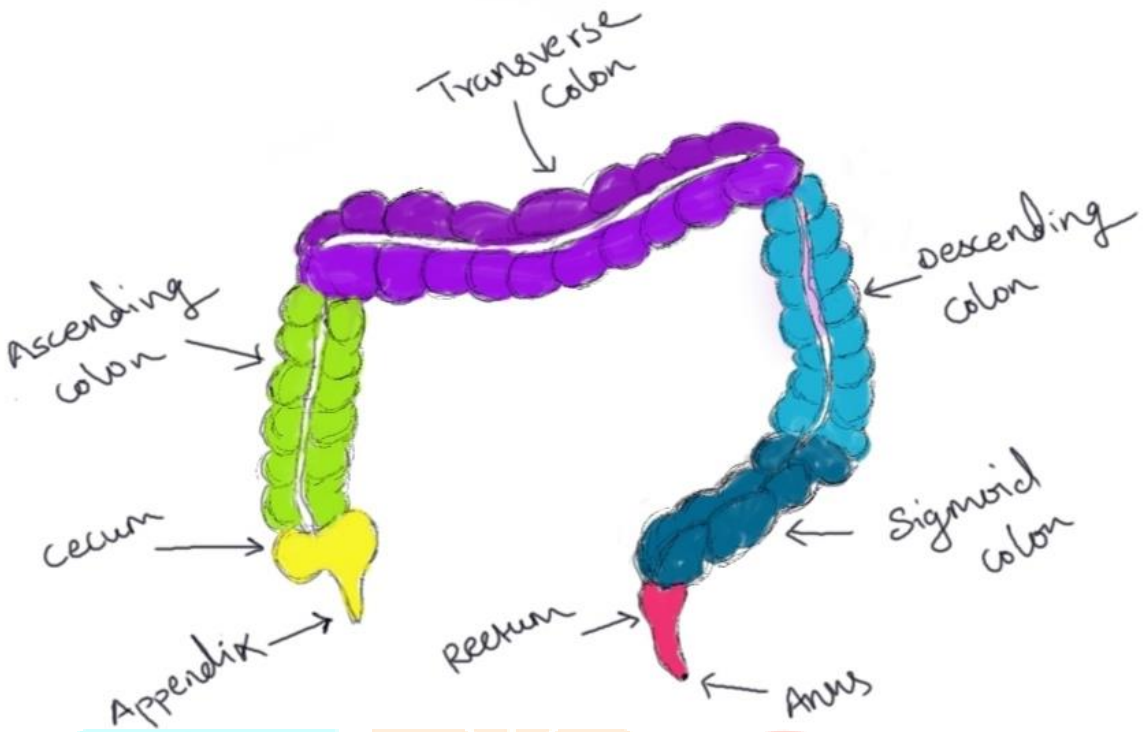


Fig.1 Anatomy of the human colon

Disorders of Colon:

1] Crohn's disease:

Parts of the digestive tract become inflamed when someone has Crohn's disease. The beginning of the large intestine and the lower end of the small intestine is where it most frequently occurs. Additionally, it can happen anywhere in the digestive tract, from the mouth to the end of the rectum (anus). An example of inflammatory bowel disease is Crohn's disease (IBD). An associated illness is an ulcerative colitis. [12] Every region of the gastrointestinal system, including the mouth and the anus, is susceptible to Crohn's disease. [13]

2] Ulcerative Colitis [UC]:

Compared to Crohn's disease, ulcerative colitis is more prevalent globally. The symptoms of ulcerative colitis may develop gradually over several weeks. It might be slightly, moderately, or highly active or can go into remission (a period when your symptoms are better). Fulminant refers to a condition that is extremely active and unresponsive to treatment. [14]

3] Colorectal cancer:

The large intestine is where colon cancer mostly develops because of the colon's ability to absorb vitamins and nutrients from the food that has been digested and passed through it. It typically begins when abnormal cells develop out of control and infiltrate the rectum's wall and surrounding tissue. One of the most prevalent cancers in adults is colorectal cancer. Given that men make up the large majority of cases, it is also one of the deadliest. Even though colorectal cancer is typically found in men, it can also affect women. [15]

4] Amoebiasis:

Entamoeba histolytica, a single-celled parasite, is the source of the infectious disease known as Amoebiasis, commonly referred to as amebic dysentery or amebic colitis (ent-a-ME-ba his-to-LI-ti-ka). People who reside in poorer countries with subpar sanitary conditions are most likely to contract the disease. Amoebiasis is more frequently detected among immigrants from developing nations in the United States. Additionally, it can be detected in people who have visited underdeveloped nations and in residents of unhygienic institutions. Guys who have intercourse with other men can contract the infection and become ill from it, though they frequently show no signs of illness. [16]

The function of the colon:

The colon is crucial when it comes to how our bodies utilize the food we eat. How food moves through the body is seen here. Food is first chewed into tiny pieces in the mouth by the teeth. After being swallowed, food passes via the esophagus and links to the stomach. Food is further processed into liquid in the stomach before moving on to the small intestine (intestine). The pancreas, liver, and gallbladder work with the small colon to continue breaking down food. All the essential vitamins and nutrients in meals are absorbed here. Most of the remaining liquid is subsequently emptied into the colon. In the colon, the water is absorbed. Colon bacteria break down the leftover substance. The remainder is then moved into the rectum by the colon. For this waste, the rectum functions as a storage container. Stool, or bodily waste, is removed from the body through the anus by rectum muscles. [17]

The important function played by the colon is

(1) The creation of an environment conducive to the development of colonic bacteria

(2) The reservoir of fecal contents;

(3) The time-appropriate expulsion of the colon's contents; and

(4) The absorption of potassium and water from the lumen, concentration of the fecal content, secretion, and excretion of potassium and bicarbonate. [18]

Factors to be considered for colonic drug delivery:

1] PH of GI tract:

The idea of utilizing pH-sensitive enteric polymers to avoid stomach medication release is well-known, and research has shown a pH gradient in distinct GI tract segments. Used to deliver drugs specifically to the colon. From the stomach to the small intestine, the pH of the GI tract rises and is prone to both inter- and intrasubject changes. The pH range of the stomach is determined by the presence or lack of food, ranging from 1.5 to 3 in the fasted state to around 4 or 5 in the fed condition. The pH of the duodenum varies between 1.7 and 4.3 when it is fed and between 3 and around 6 when it is fasting. The pH rises slightly from around 6.6 to 7.5 in the jejunum and then drops to about 6.4 in the mid-small bowel and ileum. The correct colon pH of the middle and left colons is approximately 6.6 and 7.0, respectively. [19]

2] Colonic flora:

Numerous bacteria in the GI tract are involved in the metabolism of ingested substances and contribute to the physiology and functioning of the GI tract. Only a tiny number of microorganisms, mostly Gram-positive facultative bacteria, are present in the upper region (the stomach, duodenum, and proximal ileum). The colon contains between 10 to 12 colony-forming units (CFU) per milliliter, the majority of which are anaerobic bacteria, as opposed to the stomach and proximal small bowel, which have less than 4 CFU/ml. The three most common species are Bacteroides, Bifidobacterium, and Eubacterium. Along with Clostridium Enterococci, anaerobic Gram-positive cocci, and different Enterobacteriaceae species are also found. [20]

3] Colonic PH:

Significant pH differences exist between various GIT areas. As an illustration, the pH of digestive tract contents might range from 1 to 2 in the stomach to 7.5 in the distal little intestine. From the end of the small intestine to the colon, the pH starts to rise steadily. A diet high in carbohydrates may affect the pH of the colon. This results from the colonic bacteria's fermentation of polysaccharides and subsequent production of short-chain fatty acids. Drugs made of polysaccharides may potentially change the pH of the colon. It is known that laxatives like lactulose can cause colonic bacteria to create lactic acid and lower the pH of the colon. [21]

Criteria for drug selection:

1] Drug applicant

The best candidates for these medications are those with poor gastrointestinal or intestinal absorption, such as peptides.CDDS. IBD, ulcerative colitis, diarrhea, and colon cancer medications are excellent candidates for local colon administration.

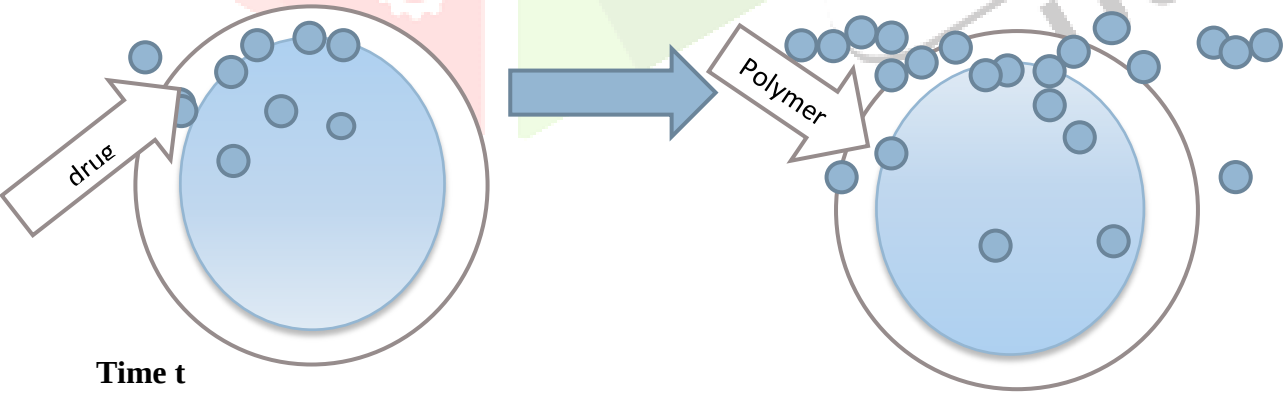
2] Drug Transporter

The physiochemical makeup of the medicine and the condition for which the system is intended to be utilized determine the best carrier for a given drug candidate. The choice of carrier is influenced by variables such as the drug's chemical makeup, stability, partition coefficient, and kind of absorption enhancer. Additionally, the functional groups of the drug molecule influence the choice of drug carrier. [22]

Approaches for colon targeting drug delivery system:

1] Timed Release Systems:

This strategy is founded on the idea of delaying medication releases until they reach the colon. While small intestine transit time is largely stable or exhibits only slight fluctuation, stomach emptying is notoriously unpredictable. The goal of creating a timed-release system is to resist the stomach's acidic environment while undergoing a delay of a predefined amount of time before the drug is released. In this instance, the time needed for the passage from the mouth to the colon is the lag time. [23]



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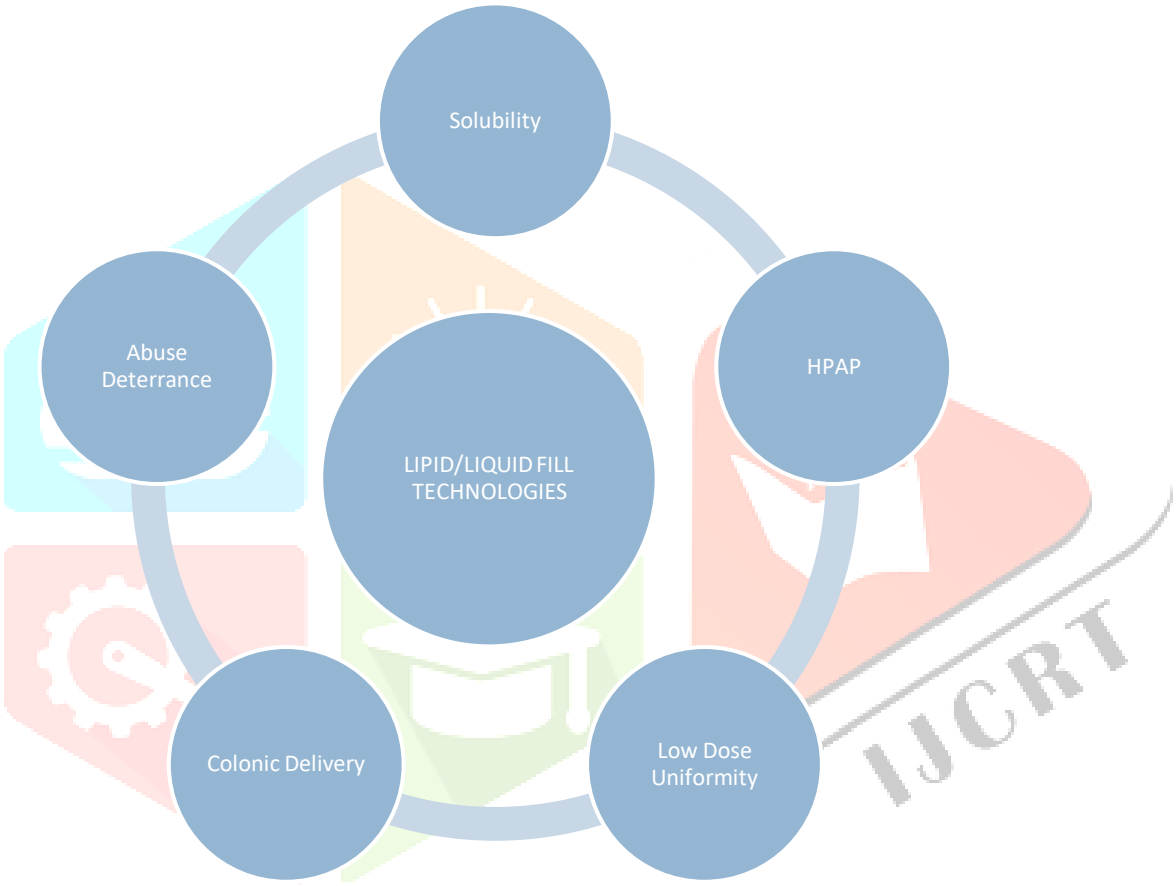
2] Coating with polymers: [pH-sensitive polymer]

The drug molecule can be coated with appropriate polymers, which only degrade in the colon, to transfer the intact molecule to the colon without absorption at the upper section of the gut. The pH-dependent systems take advantage of the widely held belief that the pH of the human GIT gradually rises from the stomach [pH 1-2 which increases to 4 during digestion], small intestine [pH 6-7] at the site of digestion, and it climbs to 7-8 in the distal ileum. The delayed release and protection against gastric fluid provided by the coating of pH-sensitive polymers on tablets, capsules, or pellets allow for use. The polymers utilized for colon targeting, however, should be able to tolerate the lower pH values of the stomach and the proximal section of the small intestine

and also be able to breakdown at the neutral or slightly alkaline pH of the terminal ileum and, preferably, at the ileocecal junction.[24]

3] Formulations Based on Lipids:

Double-layered phospholipids form the basis of the effective medication delivery system known as a liposome. Hydrophilic and lipophilic medications can be incorporated into liposomes because they are biocompatible, biodegradable, and biodegradable. To prevent liposome instability in acidic environments and to increase site-specificity, the surface of liposomes can be coated with pH-dependent polymers. Using glycol chitosan and pH-dependent Eudragit® S100 to coat the surface of anionic liposomes, Zhao et al. created colon-targeted liposomal formulations for sorafenib. The systemic exposure of sorafenib in rats was increased by these liposomes' strong stability at acidic and neutral pH and little drug leakage. In terms of drug protection and trapping effectiveness, solid lipid nanoparticles are likewise a superior solution. [25]

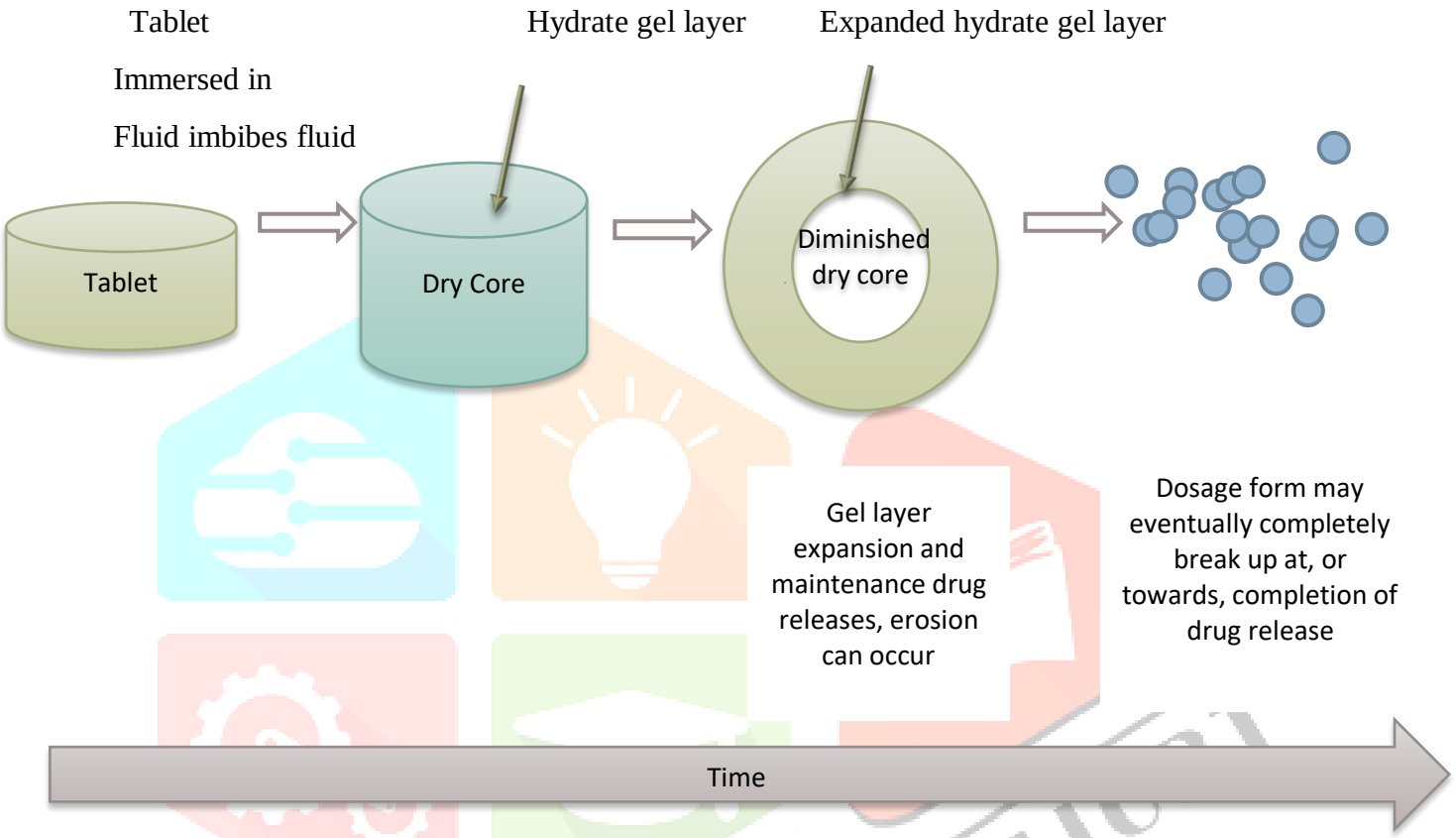


4] Prodrugs:

Prodrugs are therapeutic substances that must go through biotransformation before exerting a pharmacological activity. They are typically created to get around chemical, physical, or physiological issues. Prodrug-based systems have been widely used to direct medications to the colon. Once in the colon, the bacteria that live there create enzymes that interact with the medications to release the active moiety. The GI tract is home to a wide range of microorganisms that support its physiology and operations and participate in the metabolism of ingested substances. The resident microflora's ability to metabolize substances is influenced by age, disease severity, and the presence of antibiotics. There are very few bacteria in the upper half (the stomach, duodenum, and proximal ileum), most of which are Gram-positive facultative bacteria. [26]

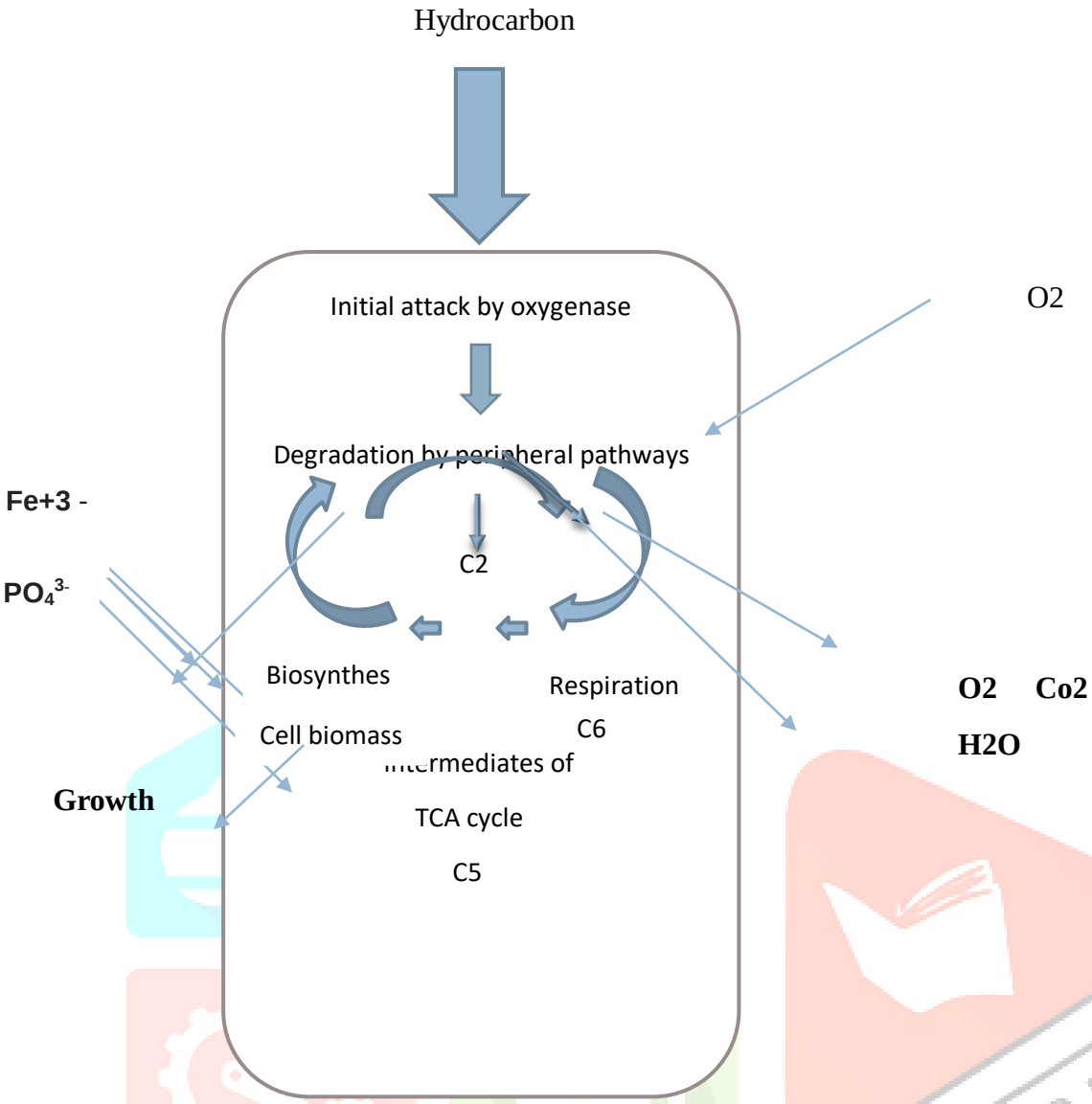
5] Tablet with hydrophilic matrix:

The active ingredient is released by surface erosion, through pores along the matrix core, or via diffusion through a swollen matrix in matrix tablets, which are solid oral dosage forms in which the drug is dispersed in compressed polymers that can maintain their shape for a considerable amount of time after ingestion. Colon targeting with matrix tablets has several benefits, including low production costs, especially in direct compression development, good reproducibility, and a well-known manufacturing method. Typically, colon target matrix tablets have a tablet core comprised of one or more polymers that can swell when in contact with water, creating a hydrogel barrier that either causes a controlled erosion of the matrix or a gradual diffusion of the medication from the core to the medium. [27]



6] Approach Dependent on Microbial Degradation:

In recent years, researchers have become increasingly interested in the use of GI microflora as a mechanism of medication release in the colonic region. Despite being dispersed throughout the GI tract, the bulk of bacteria is found in the distal intestine. The majority of colonic bacteria are anaerobic in nature, and they release enzymes that can break down both endogenous and foreign substrates like proteins and carbohydrates that bypass upper GI tract digestion. The two most prevalent modes of microbial activation in the colon are glycosidic-bond hydrolysis and azo-bond reduction. [2



Recent Advancement in Colon targeting.

1] Precision cancer medicines.

Molecular profiling has emerged as a key factor in directing clinical decisions when evaluating therapy options for individuals with metastatic colorectal cancer (mCRC). The basic base regimens used to treat mCRC are FOLFOX and FOLFIRI (fluorouracil, leucovorin plus oxaliplatin, or irinotecan, respectively). In the first-line situation, biological medicines are both safe and efficient. Examples include the vascular endothelial growth factor monoclonal antibody, bevacizumab, and the EGFR-targeted treatments cetuximab and panitumumab. It is still up for debate as to when and with which patient population these drugs will be most effective. Here, we analyze several studies that looked at how well various treatments worked in relaboututations found in colon tumors. KRAS mutations at exon 2 have been found to foretell resistance to EGFR-targeted treatments, according to early investigations. A more precise method for treating mCRC has evolved as a result of the expansion of the data to include KRAS mutations at exons 3 and 4, NRAS mutations at exons 2, 3, and 4, as well as other biomarkers like BRAF and PIK3CA. Therapy options will become more accurate and their results more efficient as our knowledge of important biomarkers grows and data from molecular profiling and treatment response become more easily accessible. [49]

Recent advancements in the management of metastatic colorectal cancer are the result of a greater understanding of the condition and careful design of each patient's regimen. The extremely significant IDEA (International Duration Evaluation of Adjuvant Chemotherapy) trial has demonstrated that the duration of adjuvant treatment can be safely shortened in a subset of patient populations. Three months of treatment with 5-fluorouracil and oxaliplatin is equivalent to six months of treatment for patients with pN1 and pT1-pT3 malignancies in terms of a 3-year survival rate. Treatment for N2 tumor patients should continue for a minimum of 6 months. The adjuvant treatment's duration being restricted greatly lowers the morbidity brought on by

chemotherapy. The use of immune-checkpoint inhibitors as an adjuvant in microsatellite-instable patients will be the subject of new studies. Immune-checkpoint suppression has a significant impact on how the disease develops. Therefore, it's critical to spot those patients right away. There is currently no novel, focused therapy options for RAS-mutant patients. There is an urgent requirement for an ideal treatment plan for those people. Epithelial growth factor receptor (EGFR) antibodies should be used as the first line of treatment for RAS wild-type patients with malignancies originating from the left side of the colon (splenic flexure to rectum). This decision was made based on a molecular and clinical marker, which significantly boosted the benefit obtained from EGFR antibodies and identified the best course of action for those individuals. Future therapeutic approaches will be influenced by new selection criteria based on gene expression, methylation, and other molecular alterations that are being investigated. [50]

Index Colorectal Lesions with Somatic Mutations in Exon 7 of the TP53 Gene Are Associated with the Early Occurrence of Metachronous Adenoma

Methods: A total of 120 patients had endoscopic therapy for advanced colorectal neoplastic that was smaller than 10 mm in diameter (the index lesion), followed by surveillance colonoscopy after 10 to 18 months. Up to 30 samples were created from a total of 143 index lesions and 84 synchronous lesions in paraffin blocks. The identification of somatic mutations at 11 hot spot gene loci was done in each of them. Statistical analysis was conducted to determine the relationship between the probability of developing a Metachronous adenoma and the mutation profiles and level of heterogeneity of the lesions. Results: Early development of Metachronous adenoma was strongly linked with a mutation in exon 7 of the TP53 gene detected in the index lesion. [51]

By promoting apoptosis and autophagy, metformin and ICG-001 work together to reverse the Chemoresistance caused by cancer stem cells in colorectal cancer.

ICG-001, a Wnt signaling inhibitor, with metformin to abort CSC-mediated Chemoresistance in CRC We found that 5FU-resistant (5FUR) CRC cells had higher levels of CSC marker expression and improved spheroid formation. Genome-wide transcriptome profiling research showed that 5FUR CRC cells were enriched in Wnt signaling, colorectal cancer metastasis signaling, etc. As a result, by reducing the expression of CSC markers and, in combination with metformin, inducing autophagy and death, selective targeting of Wnt signaling was able to reverse CSC-mediated Chemoresistance. Additionally, we noticed the anti-tumor effects of metformin and ICG-001 in tumors or ganoids produced by CRC patients. In conclusion, our research shows that the synergistic effects of metformin and ICG-001 can be used to treat CRC patients who have developed therapeutic resistance to 5FU.[52]

The liposomal formulation for the colon.

1] Orally administered liposomal formulation for colon drug delivery by Susan Hua:

Natural polymers chitosan and pectin.

Thought to be non-toxic, biodegradable, and mucoadhesive. For GI tract targeting, adhesion to the mucosa is advantageous since it encourages direct contact with the liposomes to the mucosal surface for cellular absorption and medication release, and when intestinal motility is elevated, as it is in conditions like IBD, liposome clearance is reduced. The anionic sulfonic and sialic acid residues found in the mucus matrix are considered to interact electrostatically with the cationic polymer to give natural polymers their mucoadhesive properties.

In comparison to uncoated liposomes, chitosan-coated liposome formulations have exhibited enhanced drug uptake in colon tissue ex vivo and increased stability in the simulated stomach and intestinal fluids. In vivo evaluation of orally administered pectin-coated liposomes. Mucoadhesion and absorption allowed for the demonstration of a rise in these nanoparticles' GIT mucosa residency, with barely any colloidal agglomeration. But it was discovered that most of the formulation accumulated in the small intestine, with very little uptake in the colon. To resolve this problem, colon-specific enteric coating like Eudragit may be employed.

Synthetic polymer:

A synthetic copolymer coating called Eudragit® enhances colon-targeted medication delivery when administered orally by combining the mucoadhesive and pH-dependent release techniques. Methacrylic co-polymers are called Eudragits. With different side group structures change the pH range at which they become soluble. They are frequently utilized enteric coverings for tablets and capsules in oral pharmaceutics. [53]

2]Design and development of liposomes for colon-targeted drug delivery Anand S. Gupta1, Sanjay J. Kshirsagar1, Mangesh R. Bhalekar2, and Tina Saldanha.

Since liposomes can specifically accumulate in sites of inflammation and reduce toxicity, they can be employed to treat IBD effectively. Methods: Thin film hydration was used to create liposomes. The optimization process employed statistical design. Acetic acid was used to create colitis. The ex vivo technique used was an inverted sac. IBD role model. A comparison of the histology and myeloperoxidase (MPO) activity was done. To transport the liposomes, particularly to the first segment of the colon, liposomes were created in enteric-coated capsules. The particle size ranged between 200 and 300 nm, and the entrapment effectiveness ranged between 40 and 60%. Ex vivo and in vivo research shows that liposomes accumulate more in the colon than pure medication does. After a 5h lag period, enteric-coated pills were administered the medication. Reduced lipid content and surfactant stabilization are the causes of low particle size. Vesicles become stiff at increased cholesterol levels and are unable to reorganize into smaller vesicles. A study demonstrates that the lipoidal character of the medicine and its mode of membrane transfer cause liposome accumulation to be higher than that of pure drugs.MPO decreases considerably when compared to the control group (p 0.05). The conclusion for the treatment of colon disease, enteric-coated capsules with targeted liposome release and higher liposomal drug accumulation in inflammatory areas offer better options. [54]

3] Folic acid-modified liposomal drug delivery strategy for tumor targeting of 5-fluorouracil;

The development of a liposomal formulation to target cancer cells specifically was the goal of this investigation. To deliver 5FU to cancer cells on a targeted basis, liposomes were created utilizing the thin layer approach and folic acid (FA). The produced liposomes were evaluated for encapsulation. Morphology, efficiency (EE %), and particle size. Using the CT26 cell line, cellular uptake, cytotoxicity research, and ROS production was assessed. Rat red blood cells were used in a hemolysis assay (RBCs). Additionally, tissue toxicities were researched using histological analysis and in vivo anticancer activity was used to study the effectiveness of targeted liposomes. The average particle size and EE% of liposomes were 114.00 nm and 67.88 nm, respectively. The TEM picture demonstrated the spherical shape of the liposomes. Targeted liposomes exhibit greater cellular absorption, lower IC50 (12.02 vs. 39.81 mm for liposomal and free 5FU), and more ROS generation (62271.28 vs. 2369.55 fluorescence intensity) than free drug on cancer cells. Hemolysis assay results demonstrated the drug's blood biocompatibility liposomes. Additionally, folate-targeted liposomes demonstrated superior tumor inhibition versus free drug (88.75 mm3 tumor volume vs. 210.00 mm3), and histological analysis revealed no abnormalities in the tissue. Folate targeted lfolate-targeteda reliable and secure method for colon cancer chemotherapy. [55]

Niosome drug delivery for the colon:

1] Targeting Colorectal Cancer Cells with Niosomes Systems Loaded with Two Anticancer Drugs Models; Comparative in Vitro and Anticancer Studies:

This study looked at the efficacy of incorporating both hydrophilic and hydrophobic anticancer medicines into niosomes because of their amphiphilic properties for treating CRC. Methods: A response surface was used to formulate drug-free niosomes.

The influence of cholesterol, surfactant, and surfactant type on the particle size and Z-potential of the manufactured niosomes will be studied using a D-optimal factorial design. An optimum formulation with a particle size of 194.4 15.5 nm and a Z-potential of 31.8 1.9 mV was chosen after numerical and statistical optimization to be loaded with Oxaliplatin and Paclitaxel individually in various concentrations. The drug release from the formulations with the highest entrapment efficiency (EE %), in vitro antitumor efficacy on HT-29 colon cancer cell line, and apoptotic activity were all assessed. Results: d—tocopheryl-prepared Niosomes When Oxaliplatin or Paclitaxel was added to polwasylene glycol 1000 succinate (TPGS) at a molar ratio of 4, cholesterol at a molar ratio of 2, and at a loading concentration of 1 molar ratio, the resultant Nano sized vesicles (278.5 19.7 and 251.6 18.1 nm) had Z-potential values of 32.7 1.01 and 31.69 0.98 mV and the highest EE. These formulations showed up to a 48-hour drug release and up to a twofold increase in both the in vitro cytotoxicity and apoptosis efficiency of the two medicines compared to free pharmaceuticals. Conclusion: These results imply that various you can change the formulation composition parameters to get niosomal vesicles that are Nano-sized and have a recognized Z-potential. It is possible for these niosomes to include either hydrophilic medications like Oxaliplatin or hydrophobic pharmaceuticals like Paclitaxel. As a

novel nanomicellar system, drug-loaded niosomes may improve the cellular absorption of both medicines, enhancing their cytotoxic and apoptotic effects against HT-29 colon cancer cells. Both Paclitaxel-niosomes and Oxaliplatin-niosomes might be viewed as promising new drug delivery methods with improved bioavailability for the treatment of colorectal cancer. [56]

Microemulsion Loaded Capsule for colon;

1] Beneficial anti-inflammatory effect of paeonol self-Microemulsion-loaded colon-specific capsules on

Experimental ulcerative colitis rats;

In our previous investigation, paeonol—the primary phenolic ingredient extracted from Chinese herbs—was to have anti-inflammatory effects on ulcerative colitis (UC). However, due to its poor solubility, it hasn't been able to evolve into a pharmaceutical product that is effective in treating colon illnesses. In this study, we created the phenol-loaded self-Microemulsion (Pae-SMEDDS) colon-specific delivery system (Pae-SME-CSC) and assessed it's in vitro and in vivo features, particularly its anti-inflammatory effects on UC rats. The disease activity index, colon weight/length ratio, macroscopic damage, and microscopic damage scores, as well as the anti-inflammatory effects, were assessed. IL-17, by using an EIA, the levels of IL-6 and TGF-b1 were also measured. The outcomes demonstrated that Pae-SME-CSC had favorable stability and favorable targeting properties both in vivo and in vitro. In terms of efficacy, the Pae-SME-CSC group (100 mg/kg) demonstrated better anti-UC effects (p .01 or p .05), and its anti-inflammatory effect was comparable to that of the Paeonol group (200 mg/kg) (p >.05). In contrast, the Paeonol group (100 mg/kg) did not exhibit any significant effect on UC (p >.05, compared with the model these findings suggested that the Pae-SME-CSC created was appropriate for colon-specific medication delivery. [57]

2] Low-dose oral Microemulsion ciclosporin for severe, refractory ulcerative colitis:

There were sixteen patients signed up. In 14/16 (88%), a clinical response was seen. The average clinical activity index ratings and levels of Days 0, 4, and 8 had C-reactive protein values of 11.8, 6.7, 4.1, 50.3, 19.3, and 9.7 mg/L, respectively. From days 0 to 8, the mean C0 was 149 pg/mL. On days 0 and 8, the mean creatinine clearance rates were 88 and 96 mL/min, respectively. Cilosporin was stopped in one patient due to an abrupt transaminase increase. The conclusion is Oral Microemulsion ciclosporin for severe, steroid-refractory ulcerative colitis still works effectively even when dosed for a target C0 of 100–200 mg/mL. This efficacy is comparable to that of larger, potentially more toxic doses. In this clinical scenario, oral medication should take the place of intravenous treatment. [58]

Micelles for colon drug delivery

1] Colon targeting of Celecoxib Nano mixed micelles using pulsatile drug delivery systems for the prevention of inflammatory bowel disease;

IBD, a crippling ailment marked by persistent colon inflammation that raises the risk of colon cancer, is also known as inflammatory bowel disease. Cyclooxygenase-2 inhibitor Celecoxib (CXB) demonstrated potential for the prevention of IBD. However, it has limited water solubility and is hazardous to the cardiovascular system.

Extended use here, to reduce systemic adverse effects, CXB solubility was increased using Nano-mixed micelles (NMMs), and the colon was then specifically targeted. The thin film hydration method was used to create Pluronic P123 NMMs using bile salts or hydrophilic Pluronic. Prior to and following freeze-drying, NMMs were assessed for particle size, size distribution, and zeta potential as well as for solubility improvement. In pulsatile systems, the freeze-dried NMMs were then loaded with various tablet plugs containing time-dependent polymers at different concentrations. Pluronic P123 and sodium Taurocholate (1:1) with a CXB: surfactant mixture ratio of 1:30 made up the ideal NMM. The goal release profile was attained by the pulsatile capsules, which had a tablet plug consisting of 75% Carbopol® and released 88.35% of the dose after an 8-hour lag. Lastly, Compared to conventional capsules and pulsatile capsules containing only CXB, the optimal NMM/pulsatile system showed a protective effect against experimentally-induced colitis. [59]

Patents on colon-targeted drug delivery:

1] Patent issued in the USA:

Sr.No	Patent NO	TITLE	INVENTORS	DATE OF PUBLICATION	Reference
1	USOO6039975A	colon targeted delivery system	New Jersey residents Navneet hargovindas Shah, Aruna M. Railkar, and Wantanee Phuapradit.	March 21, 2000	29
2	US 2007/0243253 A1	colonic drug delivery formulation	Abdul Wash Basit, Middlesex (GB); Valentine Chidi Ibekwe, London (GB)	Oct. 18, 2007	30

International Patent:

Sr no	Patent No	Title	Inventors	Date of publication	Reference
1	WO1991007949A1	Delayed-release formulations	Stephen Gordon Ring David Brian Archer Michael Charles Allwood John Michael Newton	1991-06-13	31
2	W01998026767A2	Site-specific controlled release dosage formulation for mesalamine.	Cesare Busetti Tiziano Crimella Vincenzo Olgiati	1998-09-03	32
3	W02001058424A1	Floating drug delivery composition	Peter James Watts Alan Smith John Russell Bond William Columbus Ian Lafferty	2001-08-16	33
4	W02005030173A1	Colon-specific drug delivery using interpolymer complexations	Clive Wilson Gour Mukherji Ashok Kumar Rampal	2005-04-07	34
5	WO2008028193A2	Colon-targeted oral formulations	Jeffrey B. Etter	2008-12-04	35

		of cytidine analogs			
6	WO2009047802A2	Novel colon targeted modified release bioadhesive formulation of 5-amino salicylic acid or its salts and metabolites thereof.	Shirish Kumar Kulkarni Rajesh Kulkarni Pandarinath Jadhav Umesh Badhe Sushma Gupta.	2009-04-16.	36
7	W02012035561A2	Improved oral targeted drug delivery system.	Monica Gulati, sima Singh, Sanjiv Duggal, Rahul Satyakam, Mamta Sharma.	2012-03-22.	37
8	W02017156214A1	Pharmaceutical compositions for colon-specific delivery.	Lianli Li.	2017-09-14.	38
9	WO95/35100	Colonic drug delivery composition	WATTS, Peter [GB/GB]; Flat 2, 47 Highfield Road, West Bridgford, Nottingham NG26DR (GB).	28 December 1995.	39
10	WO2007/122374 AS	Colonic Drug Delivery Formulation	BASIT, Abdul, Wash [GB/GB]; 55 Alicia Gardens, Harrow, Middlesex HA3 SJB (GB). IBEKWE, Valentine, Chidi [GB/GB]; 19 Springfield Road, London E15 3TR (GB).	19 March 2009	40
11	WO2009/087665A2	NoveNANDAtro retentive Drug Delivery System.	NANDE, Vishwanath, Sudhir [IN/IN]; Plot	11 December 2007.	41

			No. 119, Mahalakshmi Apartments, Nelco Society, Jaitala Road, Nagpur 440 022, Maharashtra (IN).		
12	WO2010/049433 A3	water-insoluble polymer: starch-based film coatings for colon targeting	Haeussler, Olaf [de/fr]; 632, route de strazeele, f-59270 fletre (Fr). Wils, Daniel [fr/fr]; 14 rue saint-georges le lot vil- lage, f-59190 morbecque (fr). Siepmann, juergen [de/fr]; 3, rue Maurice Schumann, f-59133 phalempin (fr). Karrout, youness [de/fr]; 26, rue newton, f-59000 Lille (fr).	23 December 2010	42
13	WO93/22334	pharmaceutical compositions and methods for colonic delivery of corticosteroid	Friend David R [US-US] 301 Gilbert Avenue	11 November 1993	43

Patent issued in Australia:

Sr No	Patent No	Title	Inventors	year of publication	Reference
1	AU2006249100B2	Colonic delivery of adsorbents	Antoin Andremont, Elias Fattal, Helene-celine HGalenicNicolas Tsapis	2012	44
2	AU2003274229B2	Gelenic formulation for colon targeted delivery of active principles	Fattal, Elias; Andremont, Antoine; couvreur, Patrick, bourgeois, sandrine	2004	45

Patent issued in European:

Sr No	Patent No	Title	Inventors	Year of publication	Reference
1	EP2081557A1	Colonic drug delivery using Zn pectin beads with a eudragit coating	Antoine A et al.	2009	46
2	EP2179727A1	Water insoluble polymer; modified derivative-based film coatings for colon targeting	Olaf H et al.	2010	47

Patent issued in Canada:

Sr No	Patent No	Title	Inventors	Year of publication	Reference
1	CA2344306 A1	Oral Drug Delivery system for enhancing the bioavailability of active form of glycyrrhizin	Kanji T	2000	48

Conclusion:

An important site for the transport and absorption of drugs is the colonic region of the GIT. CDDS provides a lot of therapeutic benefits. Benefits of both local and systemic treatment for patients. Colonic bacterial enzymes that break down natural materials are more likely to be used in systems that aim to attain colon specificity. The development and validation of a dissolution method that incorporates the physiological features of the colon while still being able to be used frequently in an industrial setting for the evaluation of CDDS present challenges for pharmaceutical scientists given the sophistication of colon-specific drug delivery systems and the uncertainty of current dissolution methods in establishing potential in-vitro/in vivo correlation.

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