Original Article

Novel Approaches For Colon Site-Specific Drug Delivery: An Overview Of Recent Advancements

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Abstract

Nowadays, various routes of administration have been explored for the effective delivery of the drug to the target site. The oral route is considered to be the most convenient for the administration of drugs to patients. But it has a serious drawback in conditions where localized delivery of the drug in the colon is required. The colon-targeted drug delivery system (CDDS) is a potential approach for systemic and topical drug delivery in treating inflammatory bowel diseases such as ulcerative colitis, Crohn's disease, colon cancer, and amoebiasis. CDDS would provide direct treatment at the site of the disease, reduced dose, and reduced systemic adverse effects. CDDS should be able to release the drug into the colon, indicating that neither drug release nor absorption should take place in the stomach or small intestine, nor should the bioactive agent be degraded there. Instead, the drug should only be released and absorbed when it reaches the colon. The colon is a site for both local and systemic drug delivery. This review mainly compares the primary approaches for CDDS (Colon Specific Drug Delivery) namely prodrugs, pH and time-dependent systems, and microbially triggered systems, which achieved limited success and had limitations as compared with newer CDDS namely pressure-controlled colonic delivery capsules, CODESTM, and osmotic controlled drug delivery systems. The review is also focused on the possible benefits and issues associated with the novel colon-targeted drug delivery system. Recent advancements in various approaches for designing colon-targeted drug delivery systems and their pharmaceutical applications are covered with a particular emphasis on formulation technologies.

Keywords: colon; non-invasive drug delivery; inflammatory bowel diseases; colorectal cancer; protein drugs, Review Drug delivery system.

1. INTRODUCTION:

Drug distribution to the colon is advantageous for treating conditions affecting the gut, like ulcerative colitis, diarrhoea, etc. Proteins and peptide medicines, which are destroyed by digestive enzymes in the gut, can also be delivered orally. The colon seems to be quite sensitive to compounds that increase the absorption of drugs with a long retention time and poor absorption.

It is a significant disadvantage when an API must to be guarded from the harsh medium of the upper GIT or when localised administration of the API to the colon is necessary. The colon is a significant source of lymphoid tissue. For instance, when an antigen is taken up by mast cells in the colonic mucosa, fast local antibody synthesis results, which aids in effective vaccine delivery. It is understood that as opposed to the stomach and small intestine, the colon has a little less pugnacious medium and reduced variety and level of activity [1,3].

For the localised treatment of numerous colonic illnesses, primarily inflammatory bowel disease (IBD), irritable bowel syndrome, and colon cancer, medication administration to specified location of lower portions of the GI tract is helpful. Chronotherapy, colon cancer prevention, and the management of nicotine addiction are a few potential uses for colonic administration. Additionally, it has grown in significance as a prospective area for the systemic administration of remedial proteins and peptides that are given intravenously. This significance extends beyond the delivery of medications for treating the local disorders.

When taken orally, these delivery systems enable medications to be released from the body when it enters the colon. By limiting the drug moieties where they are most needed, these delayed mechanisms aim to increase a drug's efficiency while minimising any possible side effects and drug stability issues brought on by early drug discharge in the upper GIT.

Due to the colon's high capacity for absorbing water, its contents are highly viscous and poorly mixed, making it difficult for most medications to reach the absorptive membrane. Enzymatic cleavage and azo reduction are frequent processes used by these gut floras. These metabolic pathways may be in charge of how various medications are metabolised. They may also be used to transport peptide-based macromolecules like insulin orally to the colon. **Table 1** lists the different diseases, medications, and sites of action that target the colon.

TABLE 1: Medicines, Location, and Conditions That Target the Colon

Location	Disease conditions	API
Topical	Inflammatory bowel disease, Irritable bowel disease	Hydrocortisone, Prednisolone, sulfasalazine
Localised	Colorectal cancer	Digestive enzyme, 5-flurouracil
Systemic	Gastric irritation	NSAID's, Insulin

The global prevalence of colonic disorders has grown throughout the last couple of decades, necessitating the development of safer, more effective, and localised pharmacological therapy. The 3rd most frequently diagnosed cancer globally, colorectal cancer (CRC) is the colonic illness that accounts for the most cancer-associated fatalities in Europe (more than 2 lakh fatalities each year) [5, 6].
Additionally, traditionally low-incidence regions like Asia are now seeing significant increases in the incidence of IBD [7]. As a result, colonic illness treatment has emerged as a crucial global public health concern.

Colon-targeted DDS have been comprehensively strived for locally treating colonic disorders because typical non-targeted therapy might have unfavourable consequences and be ineffective because the drug is absorbed systemically prior to arriving at the destined location [8, 9]. Along with topical administration, colon-targeted DDS are also useful for enhancing the bioavailability of medications gullible to enzymatic and/or acidic destabilisation in the upper GIT, like macromolecules like proteins and peptides because the colon has lower protease activity [10-12]. Even while colonic delivery of macromolecules hasn't been studied as much as colonic delivery of small molecules, future study may show that it has the potential to be a successful oral delivery strategy for macromolecules.

1.1 Advantages of colon-targeted DDS:

- Limiting the side effects associated with the treatment of colonic disorders (like Crohn's disease, colorectal cancer, and ulcerative colitis).
- By creating a more 'friendly' surrounding for peptides and proteins than the upper gut.
- Limiting the substantial first-pass metabolism.
- Avoiding the stomach irritability brought on by taking NSAIDs orally.
- Delay in medicine release for rheumatoid arthritis, angina, and asthma.

1.2 Disadvantages of colon-targeted DDS:

- Difficulty in accessing the colon.
- The liquid quantity in the colon is less and is thicker than that in the top GIT, that is the restriction for medications that are weakly soluble. For delivery to be successful, the medication needs to be in solution prior to reaching the colon.
- The smaller surface area of the colon and accompanying tighter tight junctions might make it more difficult for drugs to cross the mucosa and enter the systemic circulation [13].

1.3 Requirement of Colon-targeted DDS:

- Drugs that are specifically sent to the colon to treat the condition locally, with reduced dosages and lesser systemic side effects [14].
- Area specific DDS would enable to provide peptide and protein treatments orally; colon-specific formulation might also be utilised to elongate the delivery time [15].
- It is thought that colon-specific medication delivery systems are useful for treating colon illnesses [15].
- The colon is a location in which localised or systemic delivery might be accomplished, as well as topical treatment of inflammatory bowel illness. Sulphasalazine and glucocorticoids are frequently used to treat such inflammatory disorders [16].
- If medications were especially targeted to the colon, several additional noteworthy illnesses of the colon could even be more successfully treated.
- Drugs that are polar or vulnerable to chemical and enzymatic breakdown in the top GI tract, that is greatly influenced by hepatic metabolism, can also be delivered using formulations for colonic distribution, specifically for remedial proteins and peptides [17].

1.4 Anatomy of the Large Intestine:

Between the ileocecal junction and the anus, the large intestine is separated into 3 major sections – the rectum, anal canal, and colon. Table 2 provides measurements of the various colonic sections.

TABLE 2: Measurements of the various colonic sections [18]

Large Intestine	Length (cm)
Cecum	6-9
Ascending colon	20-25
Descending colon	10-15
Transverse colon	40-45

Sigmoid colon	35- 40
Rectum	12
Anal canal	3

From the ileum to the anus is the large intestine, which is 1.5 m in length and 6.5 cm in diameter. By means of its mesocolon, it is joined to the back abdominal wall. The four fundamentally significant portions of the large intestine are the cecum, colon, rectum, and anal canal. The ileocecal sphincter protects the entrance from the ileum into the large intestine and permits substances to move from the small intestine into the latter.

The cecum, a little pouch of 6 cm in length, hangs beneath the ileocecal valve. The colon contains the ascending, transverse, descending, and sigmoid parts and connects to the open point of the cecum by a lengthy tube. The ascending colon originates on the right flank of the abdomen and extends to the liver's menial border, and then run as the transverse colon across the abdomen to the left side. The descending colon descends inferiorly toward the iliac crest on the left side, curving below the menial edge of the spleen. The left iliac crest is where the sigmoid colon starts, and it ends at the rectum.
Located in front of the sacrum and coccyx, the rectum is the last 20 cm of the GI tract. Anal canal, 2-3 cm length, refers to the last section of the rectum. This region's mucous membrane is organised into longitudinal folds known as anal columns, each of which houses a web of arteries and veins. A smooth muscle sphincter located internally and a skeletal muscle sphincter located externally protect the anus, the entrance of the anal canal to the outside. By providing a favourable medium for the growth of different bacteria, the large intestine aids in the breakdown of proteins and carbohydrates into their simpler forms by producing a variety of enzymes. Through the osmosis-mediated absorption of water (about 100–200 mL), the large intestine contributes to the maintenance of a healthy body water balance. It also absorbs ions like salt and chloride as well as vitamins B and K.

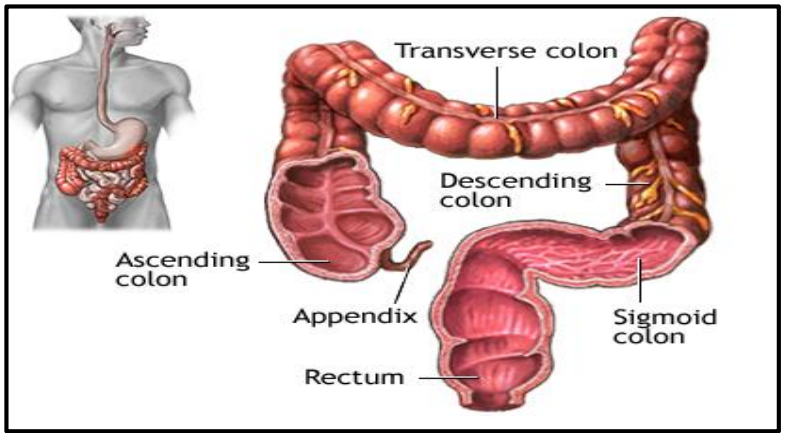

Figure 1: Structure of colon

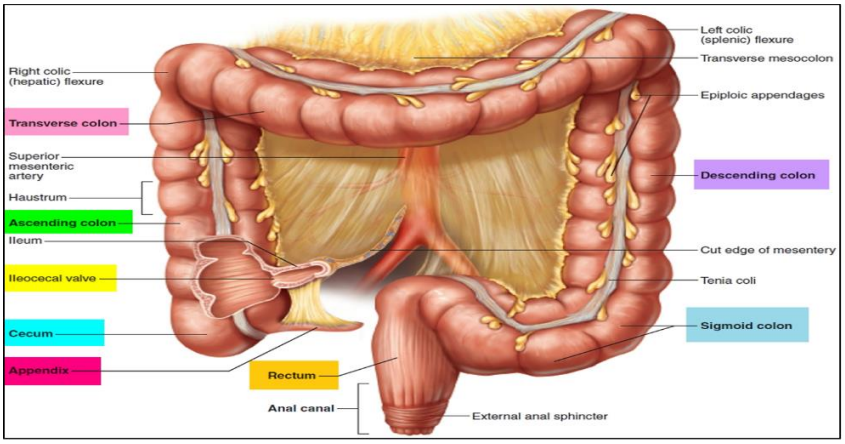

Figure 2: Anatomy of the Large Intestine

1.5 Colon-related conditions (Shown in Figure 3)

I. Crohn's Disease: Granulomatous inflammation is a symptom of persistent ulcerative IBD that is idiopathic. Any section of the GIT may be related to it, with the distal ileum or colon being the most commonly impacted segments. [19]

II. Ulcerative Colitis: Acute and long-term ulcerative inflammation of the rectum's mucosa and submucosa as well as the descending portion of the colon may be involved exhibiting a severe acute flare-up, diarrhoea, bleeding ulcers, pus drainage. [19]

III. Amoebiasis: *Entamoeba histolytica* is the cause of this infection. When a parasite in the form of a cyst wall dissolves in the small intestine, allowing amoebae to escape and enter the large intestine where they infiltrate the mucosal epithelium and eventually cause a flask-shaped ulcer in the submucosa. [20]
IV. Diverticulosis: Constipation, stomach pain and sporadic bleeding are some of the clinical symptoms of outpouching or herniation of mucosa and submucosa. [21]
V. Diverticulitis: Constipation and stomach pain are the results of this inflammatory form of diverculi [21].
VI. Colon Bleeding: There are two forms of haemorrhoidal vein varicosities – a) Internal pile: enlargement of the superior haemorrhoid plexus; b) External pile: enlargement of the inferior plexus. These result in bleeding, which is frequently noticed in the faces [22].
VII. Salmonellosis: Usually brought on by non-typhoidal salmonella after eating tainted food. Doctors use antibiotics to treat such infections when parasites infect bowel and produce diarrhoea and stomach cramps. [23]
VIII. Hirschsprung's disease: This severe kind of intestinal constipation only allows for one or two bowel movements every week. [24]
IX. Diarrhoea: Increased bowel movement and poor absorption by the intestines, along with faeces that pass through the large intestine too rapidly, are the major causes of diarrhoea. These conditions lead to dehydration and electrolyte imbalances. Lactose intolerance, stress and bacteria that bothers the gut mucosa can all contribute to excessive motility, which can occasionally self-limit.
X. Traveller's Diarrhoea: Pathogens like enterotoxigenic *Escherichia coli*, enteroaggregative *E. coli*, Salmonella, etc. cause of traveller's diarrhoea exhibiting symptoms such as nausea, vomiting, loose stool and fever. [25]
XI. Colorectal Polyps: Any growth or mass that protrudes into the lumen from the mucous membrane is referred to as a polyp, and it is more common in the large intestine and rectosigmoid colon than the proximal colon. Both neoplastic and non-neoplastic conditions can apply [26].
XII. Colon Cancer: With 639,000 recorded fatalities each year, it is the 4th most prevalent cancer globally [27].

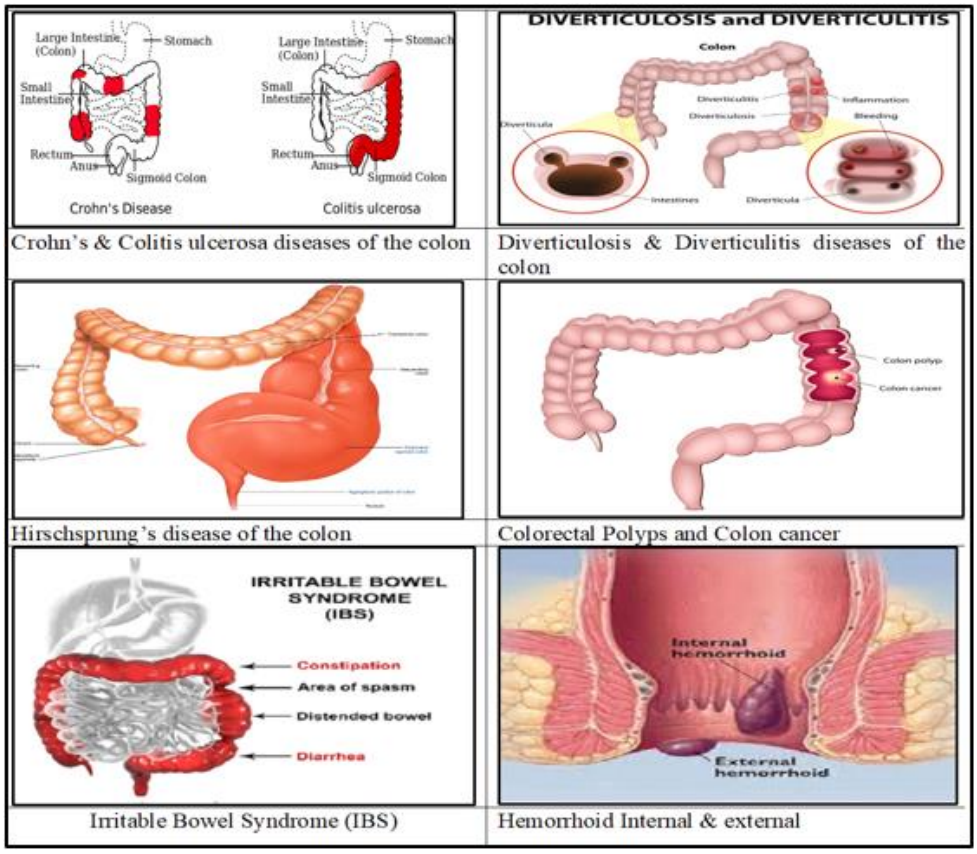

Figure 3: Different Diseases of the colon

Advantages of CDDS [28]:

1. The colon is the perfect location to administer formulations for localised colon disorders.
2. Local therapy has the benefit of using less medication overall.
3. Reduction of frequency of doses. Thus, cheaper price of costly medications.
4. The bioavailability of poorly absorbed pharmacological molecules may be enhanced in the colon.
5. Skipping of initial first-pass metabolism.
6. It has prolonged retention duration and is quite open to compounds that boost the uptake of poorly absorbed drugs.
7. Potentially reducing the frequency of adverse effects and drug interactions.
8. Enhance patient compliance.
9. Specific delivery of dosage forms.

Requirements for Drug Selection for CDDS:

Following are some explanations of the selection criteria for medications utilised in colon drug delivery. (Shown in table 3)

- The disease's pathology and pattern, particularly the lower GI tract's impacted regions.
- The drug's physical, chemical and biological characteristics, including the APIs targeted rate of release as well as its solubility, stability and permeability at the area of administration.
- Since intestinal fluid pH has an impact on the effectiveness of colon-specific DDS, it is frequently taken into account while developing delayed release formulations.
- The medications that exhibit low uptake from the gut, such as peptides, are the ideal options for CDDS.
- Another element that affects CDDS is the drug carrier. The choice of a carrier for a specific API is influenced by both the ailment for which the system is intended to be utilised and the drug's physicochemical makeup. The choice of carrier is influenced by elements such as chemical make-up, partition coefficient, medication stability and the kind of absorption enhancer used.
- The functional groups of the API's moiety determine the API's carrier of choice. For instance, an azo bond may be employed to connect a drug's aniline or nitro groups to another benzene group.

Table 3: Requirements for Drug Selection for CDDS

Criteria	Pharmacological class	Non- peptide drugs	Peptide drugs
Drugs utilised to treat GI disorders locally in the colon	Anti-inflammatory drugs	Oxyprenolol	Antisense oligonucleotide
Drugs poorly absorbed from top GIT	Antihypertensive drugs	Theophylline,	Cyclosporin
Drugs for colorectal cancer	Anti-neoplastic drugs	Pseudoephederine	Epoetin
Drugs that break down in the small intestine and stomach	Proteins and peptides	Bromophenaramine	Gonadoreline
Drugs that go through a lot of FPM	Corticosteroids	Nicotine	Protirelin

General Considerations for Colonic Formulation Design

The appropriate choice of a formulation strategy depends on the key elements below:

- The pathology and design of the illness, particularly the impacted areas of the lower GIT, or the physiology and physiological makeup of a strong colon, are not meant for targeted therapy.
- An API's biopharmaceutical and physicochemical characteristics, such as permeability, stability and solubility at the administration area.
- The preferred release pattern of the API**.**

Drugs Appropriate for CDDS

For administration through the colon, the following groups of medications are appropriate.

1. Drugs utilised for treating irritable bowel disease (IBD) needs localised administration to the colon. Ex.- sulphasalazine, mesalazine, steroids.
2. For treating colon cancer. Ex. 5- fluorouracil, methotrexate.
3. Protein and peptide drugs.
4. For treating infectious illnesses (amoebiasis) - need delivery to a precise area. Ex.- metronidazole, albendazole.
5. For treating rheumatoid arthritis (NSAIDs), nocturnal asthma and angina, there is a need of delay in absorption because of the circadian rhythm.
6. Drugs having higher selective absorption in colon in comparison to the small intestine because of small quantity of paracellular transport. Ex.- diclofenac, ibuprofen.

Different Approaches for The Colon Targeting

[A] Primary approaches for CDDS [29]

a) pH-sensitive polymer coating drug delivery to the colon
b) Delayed (time-controlled release system) release drugdelivery to the colon
c) Microbially triggered drug delivery to the colon
i. Prodrug approach
ii. Polysaccharide-based approach

[B] Newly developed approaches for CDDS [30]

a) Pressure-controlled drug delivery system (PCDCS)
b) CODES TM (a novel colon-targeted drug delivery system)
c) Osmotic controlled drug delivery to the colon (OROS-CT)
d) Pulsincap system
e) Port System
f) Time clock system
g) Chronotropic system
h) Colal-pred system
i) Target technology

j) Ticking capsule
k) Enterion capsule technology

a) pH-Dependent DDS

Colonic medicine delivery could be focused on utilizing the knowledge that the pH of the colon is greater than top GI tract. So, employing pH-dependent polymers, a colon-targeted DDS is created. Polymers like cellulose acetate phthalates (CAP), copolymers of methacrylic acid and methyl methacrylate (e.g., Eudragit® S 100) [31-34]. The optimal polymer must be soluble in the pH of the distal ileum and colon, but be in position to tolerate the low pH of the stomach and the adjoining small intestine. Because of this, it is anticipated that API delivery methods enveloped with pH-dependent polymers with a dissolving threshold of pH 6.0-7.0 will hamper API break down and avoid early API discharge in the top GI tract prior coming to the colonic locations. [35]. In light of the gigantic inter- and intra-subject variation in crucial steps, this pH-dependent approach has exhibited vast variance in drug discharge and failing in in-vivo such as pH, liquid volumes, GI transit lengths, and movability [36]. Moreover, the pH levels of the gut can remarkably be impacted by dietary reasons, medical problems, water intake, and pathogenic activity [37]. For illustration, persons with ulcerative colitis have higher acidic intestinal pH in comparison to healthy subjects, leading to inadequate delivery of medication to the target location by enteric-coated systems. Therefore, pH-dependent drug release systems may perform less effectively due to the strong pH change caused by numerous interior and exterior causes, which frequently results in poor site-specific release of drug. Eudragit® S coating wasn't acceptable for the colon-targeted drug release, according to Ibekwe et al. [38], either because the target site did not disintegrate or because the drug was released prematurely before the target area. Ibekwe et al [39]'s confirmation of the deficit of site-specific drug discharge of Eudragit® S coated tablets in upcoming human studies led them to hypothesise that the disintegration of these tablets is influenced by a variety of physical factors, like GIT pH, feed status, and intestinal transit period. There have been initiatives to integrate pH-dependent delivery systems with different distribution approaches, like time-dependent and enzyme-triggered processes, in an attempt to avoid this constraint of pH-dependent systems. To integrate pH-dependent systems with colonic microbial degradation systems, for instance, Eudragit® S and high-amylose maize starch were combined [40].

Liu et al. [41] used a dual coating strategy, speeding drug dissolution at pH > 7, by utilising an alkaline aqueous solution of Eudragit® S with buffering agents for the interior layer and an organic solution of Eudragit® S for the exterior layer. Varum et al [42]'s assessment of the in vivo behavior of this dual-coated method in people showed more consistently disintegrating dual-coated tablets, primarily in the lower gut. For the colonic administration of prednisolone, Hashem et al. [43] created microspheres incorporating time- and pH-dependent mechanisms. They increased colonic medication distribution while limiting early drug release in the start of intestine by combining Eudragit® S with ethyl cellulose. Another example of a multiple-unit technique that offers consistent and extended drug release along with targeted drug delivery to the colon is Eudracol® [44]. Nevertheless, there is always room for advancement, integrated systems consisting the various release-triggering operations are usually more beneficial to combat pathologic deviation than the pH-dependent system alone. Additionally, nano- and micro-particles have enormous potential for focused targeting inflammatory colonic regions and enhancing medication absorption.

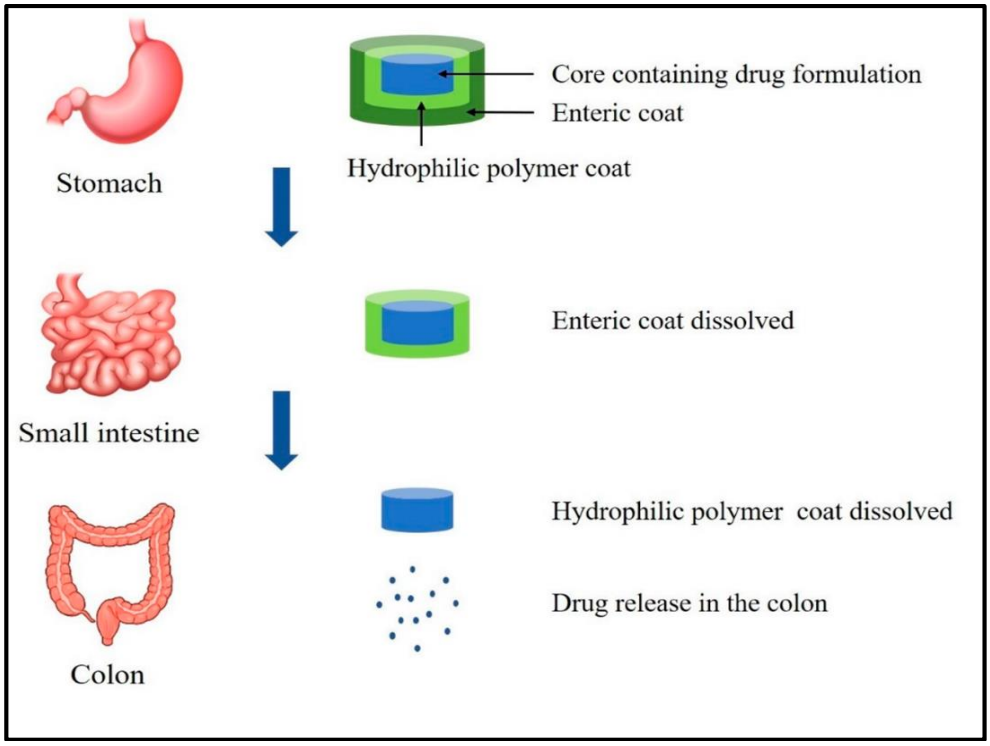

Figure 4: pH-dependent DDS

b) Time-controlled drug delivery system

It is difficult to colonise with this approach since the moving period of a formulation in the GI tract divides the area of drug discharge. By elongating the lag time by approximately 5.5 hours, the dosage form can likewise be utilised as a colon-targeting dosage form [45]. A pH-dependent (enteric coat) part is included in time-controlled formulations for colonic distribution since the transit duration of a formulation through the GI tract is regulated by the gastric emptying rate. Because additional regulated release portions rely on methods of swelling, osmosis as a mixture of two, or are frequently involved in the timely discharge, enteric coating is also utilised to obstruct lipid swelling and breakdown in the top GIT.

c) Microbially targeted drug delivery to the colon

The colon's microbiota has a concentration of 1011–1012 CFU/ml [46]. Primarily composed of anaerobic microorganisms like bacteroides, eubacteria, among others, use different kinds of substrates that are still present unprocessed in the small intestine to meet their energy needs. Examples of these include di and trisaccharides, etc. [47] For this fermentation in microflora, a large variety of enzymes are produced, including glucuroidase, deaminase, etc. Since biodegradable enzymes are exclusively present in the colon, using biodegradable polymers for colon-specific medication delivery appears to be a more focused strategy than other strategies. These polymers enable the delivery of the medicine to the colon while protecting it from the media of the top gut. On arriving at the colon, they are assimilated by microbes, degraded by an enzyme, and have the polymer backbone broken, all of which caused a lowering in their molar mass and a corresponding reduction in mechanical strength [48-52].

i. Prodrug approach

A prodrug is a pharmacologically inert derivative of a parent drug moiety that is necessitated to undergo impulsive or enzymatic conversion in vitro to produce an active drug. The prodrugs are made to liberate the active drug component from the drug carrier through enzymatic hydrolysis in the colon after negligible uptake and hydrolysis in the top GIT. The metabolism of azo compounds by intestinal bacteria is among the most thoroughly researched bacterial metabolic procedures [53]. With the medication coupled to hydrophobic moieties such amino acids, glucose, etc., additional connections that are sensitive to bacterial hydrolysis, particularly in the colon, have been created. The prodrug approach's drawback is that it isn’t very adaptable because its formulation relies on the functional groups that are accessible on the drug moiety for chemical coupling.

ii. Polysaccharide based drug delivery system

Given that these polymers are plentiful, affordable, and available in a variety of forms with a variety of characteristics, they are of interest for drugs that target the colon. They form gels easily and are extremely durable, non-toxic, hydrophobic, and biodegradable. Colonic bacteria convert them into simple saccharides [54]. Therefore, they qualify as "Generally Regarded As Safe" (GRAS).

B] NEWLY DESIGNED STRATEGIES FOR CDDS:

a) Pressure-controlled drug delivery system

The colon experiences greater pressures than the small intestine due to peristalsis. By employing the insoluble in water material ethyl cellulose, Takaya et al. created pressure-controlled colon-delivery capsules [55]. As there is pressure in the colon's lumen, in such systems, medication release happens when a water-insoluble polymer capsule dissolves. The main factor in the formulation's breaking down is the width of the ethyl cellulose membrane [56, 57]. The procedure also appears to be impacted by capsule density and size. The colon's luminal matter has a higher viscosity than the small intestine's due to the reabsorption of water from the colon. Therefore, it has been determined that oral drug delivery methods for the colon may have issues due to drug disintegration in the colon. The medication is in a fluid form in pressure-controlled ethyl cellulose single-unit capsules. [58] When pressure-controlled capsules were given to people, lag durations of 3 to 5 hours in terms of medication uptake were observed.

b) Novel Colon Targeted Drug Delivery System(Codestm)

Since pH- or time-dependent systems have their own set of challenges, CODESTM is a special CDDS technique that was created to address those issues [59, 60]. The CODESTM technique combines pH-dependent and microbially driven CDDS. It was created by utilising an original method incorporating lactulose, which serves as a catalyst for colonic drug release that is targeted to a particular spot (Fig. 5). The approach comprises of a usual tablet core of lactulose that is then covered in an acid-soluble substance called Eudragit E and an enteric matter called Eudragit L. The idea behind the technique is that the enteric coating, which shields the pill while it's in the stomach, will swiftly dissolve after gastric emptying. The preparation is then shielded by the coating's acid-soluble substance as it travels through the small intestine's alkaline pH [61]. When the tablet enters the colon, the bacteria breaks down the polysaccharide (lactulose) into organic acid using enzymes. This leads to a sufficient drop in pH around the system to cause the coating’s disintegration and subsequent medication release.

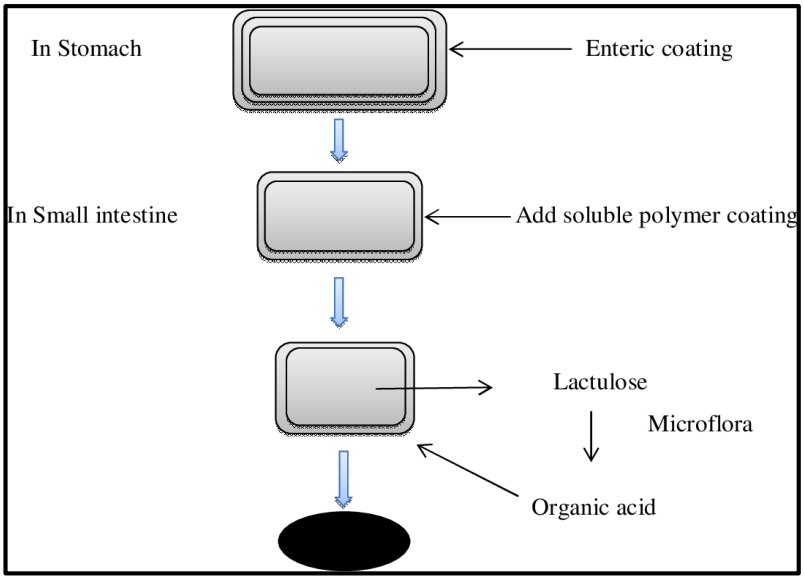

Figure 5: Schematic design of CODES system.

Osmotic Controlled Drug Delivery (Oros-Ct) (Shown in figure 6)

To treat a condition locally in the colon or to obtain systemic uptake that would otherwise be perplexing, the OROS-CT (Alza corporation) can be employed [62]. The OROS-CT system contains just one osmotic unit or as many as five or six push-pull units, each four millimetres in diameter and confined in a hard gelatin capsule (Fig. 6) [63]. An osmotic push layer and a drug layer are both present in each bilayer push-pull unit, and both are encircled by a semipermeable membrane. Near the medication layer, a hole is punched through the membrane. The push-pull unit capsule made of gelatin dissolves right away after the OROS-CT is ingested. Each push-pull unit is unable to absorb water in the acidic aqueous medium of the stomach owing to its drug-impermeable enteric coating, thus no medicine is administered. When the device reaches the small intestine, the coating solubilizes in the environment's greater pH (pH > 7), permitting water to access the device. This swelling of the osmotic push section results in the creation of a flowable gel in the drug partition. Drug gel is expelled forcibly of the aperture by swelling of the osmotic push section at a pace that is precisely regulated by the speed of water transport across the selectively permeable membrane. To ignore drug administration in the small intestine when treating ulcerative colitis, each push-pull device is built with a 3–4-hour post gastric stalling. When the unit enters the colon, the drug starts to release. In the colon, OROS-CT devices can deliver medications over a time span as short as four hours or can keep a steady release rate for up to 24 hours. New phase transited systems have recently popped up, and they look to be a useful tool for colon drug targeting [64-67]. To examine the effectiveness and stability of CDDS, numerous in vitro and in vivo examination methodologies have been made and recommended.

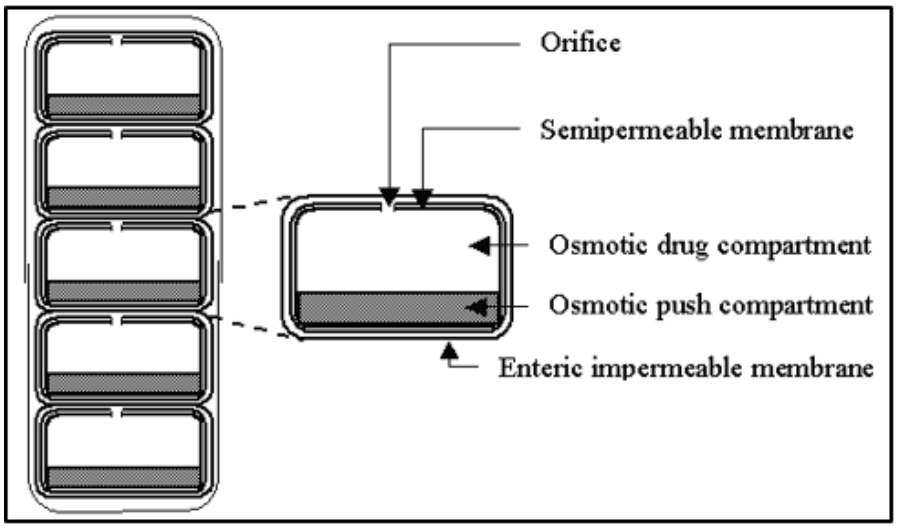

Figure 6: An illustration of the OROS-CT colon-targeted drug delivery device.

c) Pulsincap System

A water-insoluble capsule encasing the drug reservoir makes up this method. To encapsulate the medicine inside the capsule body, a hydrogel plug that expands was utilised [68]. This capsule swelled when it came into touch with the dissolution fluid, and after a delay, the plug forced itself out of the capsule and promptly discharged the medication. Discrete viscosity classes of HPMC, PVA, and polyethylene oxide were employed as polymers in the creation of the hydrogel plug. Lag time was managed by the plug's length and point of insertion into the capsule.

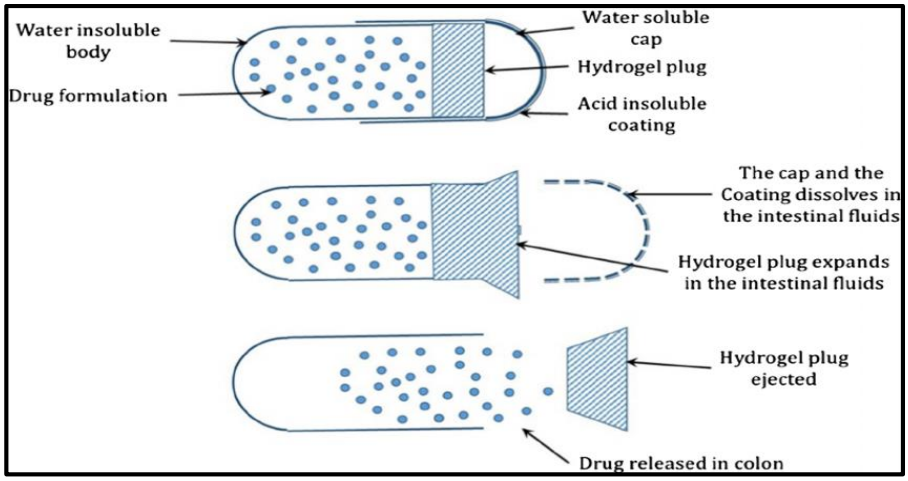

Figure 7: An illustration of the pulsincap colon-targeted medication delivery system's mechanics

d) Port System

It comprises of an insoluble plug made of a medication formulation and an osmotically active substance [69]. Human system demonstrates better in-vivo and in-vitro correlation.

e) Time Clock System

It is a delivery system focused on an aqueous dispersion-coated solid formulation [70]. To increase adherence to the core, a water-soluble polymer is introduced to this hydrophobic surfactant layer coating. The dispersion rehydrates and redisperses when it comes into touch with dissolving fluid. Modifying the film's thickness could alter the lag time. The core quickly discharges the API following the delay or the time taken for rehydration.

f) Chronotropic System

These systems work by surrounding the drug reservoir with a dissolving barrier layer, which dissolves over time and causes the drug to release all at once. The core of a chronotropic system is a reservoir coated with the hydrophilic polymer HPMC [71–73]. To combat intrasubject variation in stomach emptying rate, an extra enteric coated film is provided on top of this layer [74].

g) Colal-Pred System

It was created by combining an authorised generic steroid (Prednisolone sodium metasulfo benzoate) to Alizyme's proprietary COLAL colonic drug delivery technology. Without the usual adverse effects of steroids, it effectively treats ulcerative colitis. It has a covering that only the bacteria found in the colon can degrade.

h) Target Technology

It is for the targeted release of medications into the colon, specifically for site-specific drug delivery in the GIT. The method works by covering injection-molded starch capsules with pH-sensitive materials.

i) Ticking Capsule

It is a chronotropic device that uses some electrical methods of managing pulsatile medication release along with digital time. It has three divisions: a battery, an electronic control device, and a porous Si-based medication delivery module. Numerous human diseases and their symptoms exhibit a predictable pattern, including hypertension at dawn, arthritic pain in the middle of the day, heart attacks at dawn and late noon, and asthma attacks (night).

j) Enterion Capsule Technology

It is a round-ended, 32 mm in length capsule that holds a drug reservoir with a space of roughly a ml. By a 9mm-diameter aperture, capsules could be filled with both a fluid and a particulate mixture. The capsules are then secured by putting a push-on cap with a silicone O-ring. By putting an external oscillating magnetic field, the components of the capsule are vigorously expelled when it reaches the desired position in the digestive tract. The frequency of the magnetic field is tuned to the low MHz range, which is adequately low for body tissues to absorb very little energy while being adequately high to produce insufficient power in a turned coil antenna placed in the capsule wall. A tiny heating resistor in a discrete sealed electronics part in the capsule receives power from the magnetic field that is produced in the coil. Heater size (less than 1mm3) indicates that heat accumulation happens very quickly. The restraining filament is in direct contact with the heater resistor, which makes it weaker and more brittle as the temperature rises. This causes the spring to loosen and the piston to move. As a result, the pressure inside the drug reservoir rises, causing the o-ring sealed cap to come off and quickly discharge the drug in gut.

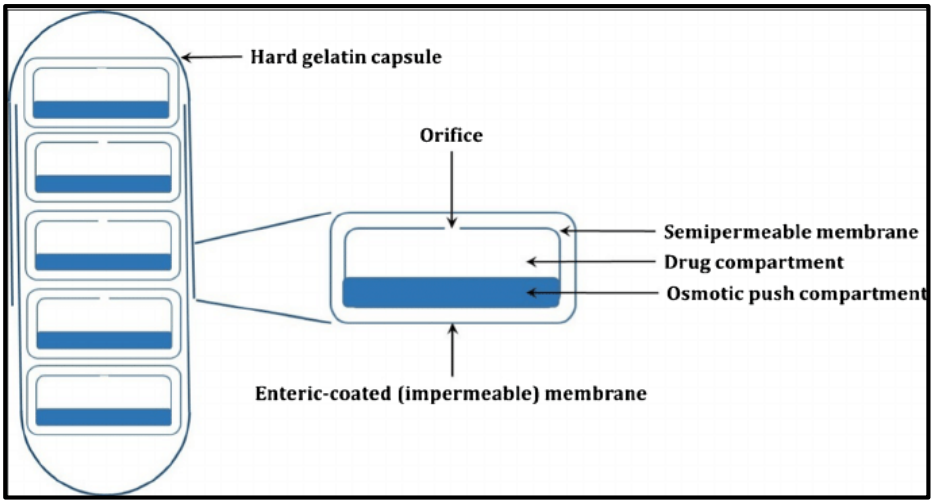

Figure 8: Enteric-coated Capsule technology

RECENT ADVANCEMENTS AND APPROACHES FOR COLON DRUG DELIVERY SYSTEMS

1. Polymer-Based Nano-/Micro-Particles [75,76]

For the colon-targeted distribution of curcumin nanoparticles, Mutalik et al. [77] used distinctive pH-sensitive hydrolyzed polyacrylamide-grafted-xanthan gum (PAAm-g-XG). Additionally, the medication liberation rate can be regulated using a mixed combination of two distinct pH-sensitive polymers. By combining Eudragit® L100 and Eudragit® S100 for successful colonic immunisation, Sahu and Pandey [78] produced the HBsAg-loaded nanoparticles, affirming the efficient distribution of nanoparticles at the colon as well as the increased immune response [78].

2. Lipid-Based Formulations

Bi-layered phospholipids are liposomes, an efficient drug delivery method [80]. APIs that are hydrophilic or lipophilic could be incorporated into liposomes because they are biodegradable, biocompatible, and flexible [81, 82]. In regards to drug preservation, trapping effeciency, and enhancing the quantity of medication liberated at certain areas, SLN are also a better solution [84, 85]. Extended drug release is possible due to the solid lipid nanoparticles' sluggish lipid matrix degradation.

Self-micro emulsifying drug delivery systems (SMEDDS), that may be helpful in the creation of colon-targeted DDS, offer enormous promise for improving the oral bioavailability of varying hydrophobic medicines [86-90]. Curcumin-consisting folate-modified SMEDDS (FSMEDDS) were prepared by Zhang et al. [91] and placed inside soft capsules covered by Eudragit® S 100.

Enzyme-Sensitive Drug Delivery Systems

Polysaccharide-Based Systems

Because of the speedy growth in microbiota and the relative enzyme action in the bottom GI tract, microbiota-activated delivery techniques have showed potential in colon-targeted medication delivery [92]. For colonic drug delivery methods, novel polysaccharides including arabinoxylans and agave fructans have also been investigated recently [93, 94]. Moreover, site selectivity, stability, and drug release behaviour can all be enhanced by structurally different polysaccharides [95]. The mucoadhesiveness of polysaccharides can be helpful for drug absorption by allowing for extended contact betwixt the mucosal surface and drug delivery agents. The merits of polysaccharide-based delivery process are their broad presence, easy fabrication, low toxicity and immunogenicity, excellent biocompatibility, and biodegradability [96]. The enormous diversity of polysaccharide molar masses and chemistry are two possible disadvantages of polysaccharide-based delivery systems, albeit [96, 97]. Additionally, polysaccharides' limited solubility in the majority of organic solvents restricts their ability to be chemically modified, while their hydrophilicity and high water solubility could lead to a hasty and unfavourable API discharge in the starting of gut [97, 98].

Cross-linking agents are routinely utilised to address this concern. Moreover, polysaccharides' usage colonic medication delivery is restricted by their incapability to produce films in addition to their swelling and solubility feature. By integrating polysaccharides and polymers, polysaccharide-based solutions could be prepared to fix these issues in addition to suppressing the hasty medication discharge in the top GI tract. For the transport of medications into the colon, water-insoluble polymers like Eudragit RS and ethyl cellulose are constantly utilised [99]. The type and amount of polysaccharides in the mixed mixture affect how quickly a medication is released. Lately, Song et al. [100] created an oral drug delivery device for orthotopic colon cancer therapy featuring programmable drug release and magnetic resonance imaging features. They chose chitosan (CS), an enzyme-sensitive moiety degradable by _-glycosidase in the colon, and polyacrylic acid (PAA), a pH-responsive polymer, both of which were tethered on Gd3+-doped mesoporous hydroxyapatite nanoparticles (Gd-MHAp-NPs).

Phloral® Technology

Ibekwe et al. described a unique colonic coating technique that combined pH-dependent and bacterially-triggered systems into a single-layer matrix film. A blend of Eudragit S and biodegradable polysaccharides were utilised to film-coat the tablets. The constant breaking down of these pills in the colon, irrespective of feeding status, was validated by a gamma scintigraphy study in healthy subjects, that brings the probability that this dual-mechanism coating might be capable of overcoming the demerits of single trigger systems and intensify colonic drug targeting. The accurate and risk-free medication discharge in the colon in both healthy and pathological states was further shown with Phloral® (Figure 9) coating technology [101]. Regardless of whether the pH-dependent polymer's dissolving threshold is not achieved, the enzyme-sensitive part will still be degraded autonomously by enzymes produced by the intestinal microbiota. The demerits of customary pH-dependent systems are resolved by this supplementary fail-safe technique. Clinical trials have supported this ground-breaking technique's constant medication delivery and lowered intra-subject variation in sick and strong participants [102].

It could be utilised for the oral administration of macromolecules like proteins, peptides, and vaccinations. Dodoo et al. [103] have examined the potential of utilising this technique to administer probiotics to the colon. While the unencapsulated probiotics displayed less patience to the gastrointestinal milieu, these capsules maintained 90% of their viability after being subjected to it for two hours.

Opticore, short for "optimised colonic release," is a cutting-edge coating technique derived from starch. It utilises pH-triggered and enzymatic-triggered discharge and was designed utilising Phloral® technique.

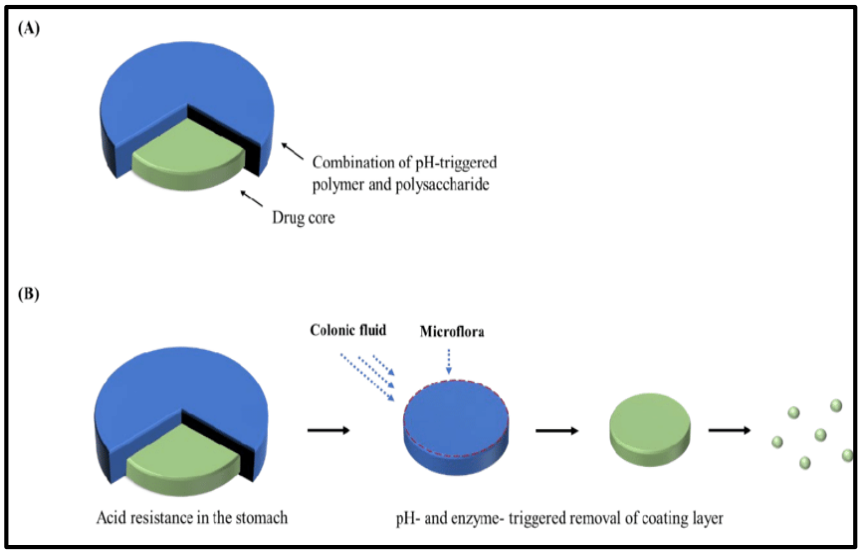

Figure 9: Phloral® tablet (A) in a schematic representation along with the medication release from the tablet (B).

Ligand/Receptor-Mediated Drug Delivery System

The utilisation of ligand/receptor-mediated systems, that boosts target selectivity by engaging with particular receptors represented at illness sites and targeting ligands on the carrier surface, has been researched for a more efficacious localised remedy of colonic illness with minimal toxic side effects (figure 10) [105]. These ligands are selected according to the functional expression profiles of precise receptors/proteins at the target cells/organs. The following is a list of ligands utilised in colon-specific delivery.

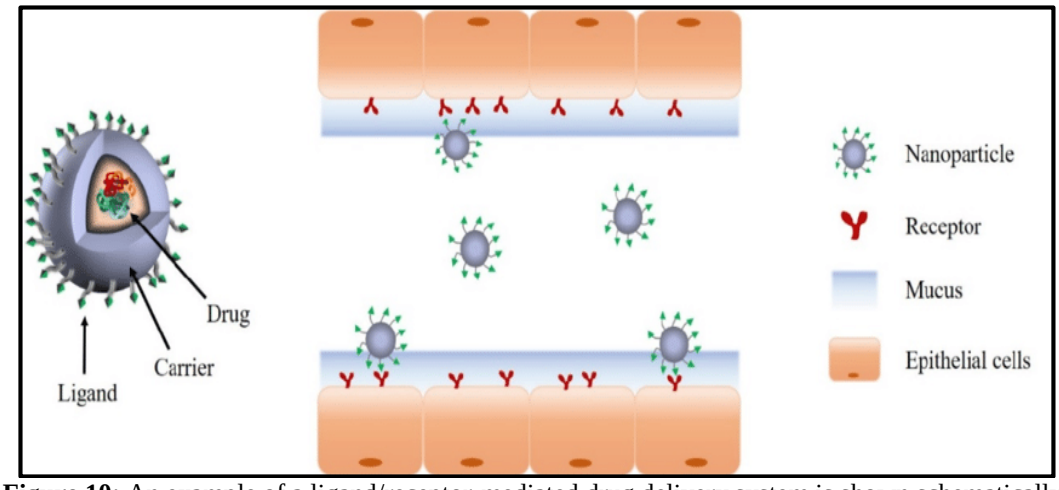

Figure 10: An example of a ligand/receptor-mediated drug delivery system is shown schematically.

2.3.1. Antibodies.

Anti-transferrin receptor antibody-conjugated liposomes were created by Harel et al. [106], who showed that they were more effectively internalised by cells than unconjugated liposomes. Additionally, anti-transferrin receptor antibody-conjugated liposomes showed favoured transport to the inflamed mucosa instead of the healthy mucosa, leading to an increased aggregation at the site of inflammation in comparison to healthy mucosa. Mice with colitis overexpress the heterodimeric neutral amino acid transporter CD98 in their colonic epithelial cells and intestinal macrophages. A strong affection for CD98-overexpressed cells was demonstrated by scCD98-functionalized nanoparticles. Nanoparticles functionalized with scCD98 and incorporating CD98 siRNA (siCD98) lessened the intensity of colitis and the amount of CD98 expression in animals with the condition [107].

2.3.2. Folic Acid

Due to the overexpression of the folate receptor in a variety of malignancies, the water-soluble vitamin folic acid is a tumor-selective targeting ligand [108]. Numerous studies have displayed that folic acid-adorned nanoparticles can promote tumor-selective medication absorption. For instance, Xiong et al. [109] showed that folic acid-conjugated liposomes enhanced daunorubicin's anti-cancer action by promoting drug absorption through the folate receptor. Additionally, folic acid (FA)-conjugated liposomes consisting 5-fluorouracil were created by Handali et al. [110]. (5-FU). When compared to free medicines, 5-FU loaded FA-liposomes showed greater cytotoxicity and considerably decreased tumor size. According to these findings, folic acid-targeted liposomes could be useful drug delivery system that might improve targeted drug delivery to cancer cells. A folate-modified SMEDDS (FSMEDDS) including curcumin was previously studied by Zhang et al. as a technique of enhancing medication solubility and distribution to the colon. Their findings demonstrated that FSMEDDS may effectively enter the colon and quickly release its pharmacological contents. An FSMEDDS could be a suitable vehicle for the distribution of curcumin to the colon since it can actively target tumour cells that overexpress folate receptors.

2.3.3. Hyaluronic Acid

A polysaccharide found in nature, hyaluronic acid (HA) includes N-acetyl-d-glucosamine and d-glucuronic acid disaccharide units. As CD44 is overexpressed in many malignancies and HA has a strong attraction for it, target-selective drug administration using HA-conjugated drug delivery devices has been investigated [111]. For instance, earlier research [111,112] looked at the efficiency of mesoporous silica nanoparticles enhanced with HA in focusing on cancer cells that overexpress CD44. In order to target inflamed intestinal mucosa, Vafaei et al. [113] created self-assembled HA nanoparticles for colonic delivery of budesonide. In light of this, HA-conjugated nanoparticles seem to be a potential method for delivering targeted drugs for the therapy of IBD. To develop a synergistic, targeted DDS for colon cancer therapy, Xiao et al. [114] researched a combination chemotherapy based on HA nanoparticles. Significant cancer-targeting capacity was demonstrated by HA-CPT/CUR-NPs against Colon-26 cells. Additionally, they looked into the combined administration of curcumin (CUR) and CD98 siRNA (siCD98) utilising polymeric nanoparticles functionalized with hyaluronic acid (HA) [115].

Lately, Prajapati et al. [116] created GEM/HA-PEG-MWCNTs, which are HA-conjugated PEGylated multi-walled carbon nanotubes that carry gemcitabine, to treat colon cancer. PEGylated multiwalled carbon nanotubes had HA linked to their surface (MWCNTs). This formulation demonstrated positive prospects for efficient colon cancer targeting.

2.3.4. Peptides

Peptide is receiving a lot of interest as a possible ligand for the delivery of targeted drugs. Biocompatibility, economic, chemical variety, and stimulus responsiveness are only a few benefits that peptides have [117, 118]. Additionally, because of the vast binding surfaces with receptors, peptide ligands demonstrate substantially better sensitivity and selectivity in comparison to small molecule ligands [119, 120]. Because they are readily available for high-throughput testing and their simplicity in production utilising automated solid-phase peptide synthesis equipment, peptide ligands are also beneficial. Additionally, the utilisation of peptide ligands in targeted DDS is encouraged by the possibility of overcoming the metabolic disturbance caused by proteases through alteration of the peptide sequences. In particular, tumor-targeted medication delivery using peptide-conjugated delivery systems is investigated. For instance, Ren et al. [121] examined the use of a synthetic 12-residue peptide (TWYKIAFQRNRK, TK peptide) for the transport of anticancer medications to the colon. TK has a strong affinity for the integrin 6_1 subtype, which is overexpressed in human colon cancer cells. As a result, TK peptide was attached as a targeting ligand to PEG-PLA micelles that contained doxorubicin. The TK peptide may be a potential targeting ligand for colon-targeted therapy because these TK-conjugated micelles demonstrated noticeably higher cytotoxicity and more successfully pierced the tumour spheroids.

2.4. Magnetically-Driven Drug Delivery System

Innovative formulations for targeted and regulated drug administration use magnetic microcarriers, like magnetic emulsions, liposomes, etc. (Figure 11). Grifantini et al. [123] constructed two discrete novel DDS with magnetic characteristics to amplify the targeted therapies of colorectal cancer. Two approaches were found to be highly successful at destroying colon cancer cells and preventing the spread of the disease at much lower antibody levels. This work showed that magnetically-driven drug delivery devices can enhance the bioavailability and target specificity, providing a new route for colon-targeted drug administration. Lately, Kono et al. [125] created magnetically-directed cell delivery methods using RAW264 murine macrophage-like cells and SPIONs and pDNA.

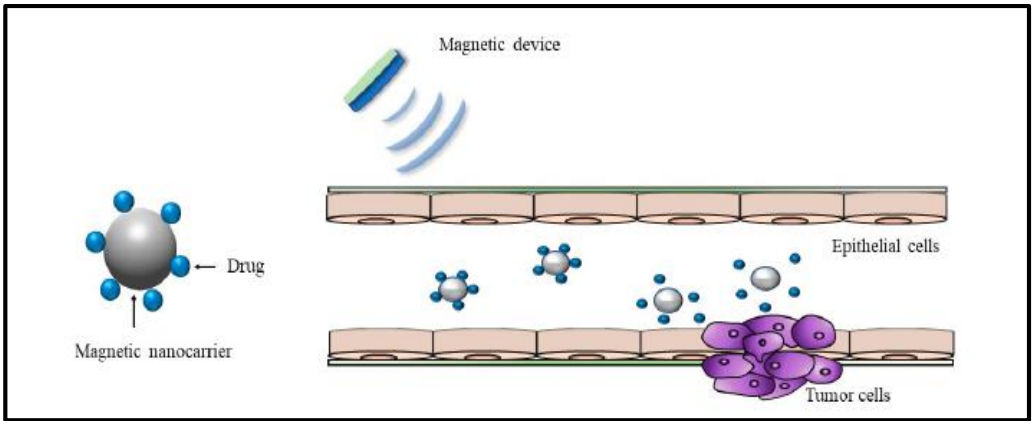

Figure 11: Magnetic nanocarrier medication delivery device illustrated schematically.

3. EVALUATION TEST OF COLON DRUG DELIVERY SYSTEM:

Since an ideal in vitro model must have the in-vivo parameters of GIT, no standardised evaluation methodology is accessible for the assessment of CDDS. The construction of an accurate in-vitro model is challenging because these variables are typically modified by food and physical stress.

a) In-vitro dissolution test

Controlled-release formulations utilised for colon-specific drug delivery typically have complex dissolution processes, and the USP-discussed procedures couldn't accurately replicate in vivo factors including pH, bacterial habitat, and mixing pressures [126]. The traditional basket technique can be utilised to perform dissolution tests for CDDS. A formulation designed specifically for the colon was tested for dissolution in a variety of media that mimicked pH levels and timeframes that would typically be present at different points throughout the digestive tract [127].

For instance, pH 1.2 media was used to mimic gastric fluid, pH 6.8 media was used to mimic the jejunal portion of the small intestine, and pH 7.2 media was used to mimic the ileum portion. A gradient dissolving research in three buffers has been conducted to evaluate enteric-coated capsules for CDDS. The capsules were assessed at pH 1.2 for two hours, pH 6.8 for an hour, and pH 7.4 for the last hour [128].

b) In-vitro enzymatic tests

Incubate the drug delivery device in a fermenter with bacteria-friendly media (*Strectococcus faccium* and *B. ovatus*). It is calculated how much drug will be released at each time slot. A buffer media containing enzymes (ezypectinase, dextranase), or rat, guinea pig, is used for drug release studies. The rate of breakdown of the polymer carrier is directly linked to the quantity of medicine delivered during a specific period of time.

c) In-vivo evaluation

Since they closely mirror the anatomical and physiological parameters in addition to the microbiology of the human GIT, a number of animals, like guinea pigs, rats, etc., are utilized to examine the transport of medicines to the colon. The relative model for colonic illnesses must be taken into account while choosing a method for assessing a CDDS.

For exploratory IBD models, guinea pigs are constantly utilised. The dispersion of glucouronidase and azoreductase operation in the gut of rats and rabbits is nearly equivalent to that of humans [129]. An innovative concept has been devised for a rapid assessment of CDDS. In this model, a subcutaneous tullel on the back of thymic nude mice is implanted with human foetal intestine, that develops a mucosal immune system from the host after 4 weeks and vascularizes within that time.

Colon-specific DDS are clinically evaluated using the Drug Delivery Index (DDI) (RCE/RSC) and when oral colonic prodrugs are administered in one or several doses, the DDI is a computed pharmacokinetic variable. Better intestinal medication delivery is indicated by a high drug DDI value. Colonoscopy and intubation are utilised to examine drug uptake from the colon. Presently, the most popular methods utilised to assess colon medicine delivery systems are gamma scintigraphy and high-frequency capsules.

4. CONCLUSION

A crucial strategy for much productive localised therapy of colonic illnesses like IBD and colorectal cancer is colon-targeted drug delivery. In regards to safety, efficiency, and patient compliance, this might provide many merits over familial dosage forms. Moreover, this technique can enhance the systemic vulnerability of APIs that are enzyme- and/or acid-labile, particularly macromolecules. So as to elevate the oral bioavailability of macromolecules, colon-targeted delivery methods are generating huge attention as an productive formulation approach. The idea of directing the supply of particular medications to the colon is self-explanatory, and there is enough scientific evidence to justify explanation. In an effort to comprehend and accomplish the ultimate purpose of targeting distribution to a particular organ, the colon,

various strategies are being studied. All currently employed methods have their own drawbacks and benefits, and in-depth investigation is concentrating on these to advance further. Because of the varying GI tract transit time, time-dependent systems are not highly practical solutions, although they might play a part in disorders that are affected by circadian rhythm. Although pressure-controlled devices have a lot of potential, the luminal pressures of different GI tract locations are not well understood. The only mechanism that exists right now is dependent on pH, yet even this system may be able to administer the medicine. Various formulation strategies to create efficient colon-targeted delivery systems were covered in this review along with certain case studies. Each of these formulation processes has benefits and drawbacks of its own, necessitating ongoing improvement to increase therapeutic effectiveness. It is essential to consider the physiological and pathological features of the colon as well as the milieu around the illness site for the construction of colon-targeted DDS to be successful. Existing dissolving procedures are ineffective for the system's in vitro assessment. The development of appropriate dissolution techniques is being studied in order to assess colon-targeted DDS.

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