Advances in Colon Cancer Treatment Through Disease Overview and Targeted Drug Delivery Approaches

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Abstract

Since colon cancer is still one of the most common and deadly cancers in the world, new treatment approaches are required for increased effectiveness and decreased systemic toxicity. Adverse effects, nonspecific distribution, and low absorption are some of the problems with conventional chemotherapy. medication delivery methods based on nanotechnology present intriguing solutions because of their improved medication stability, controlled release, and targeted distribution. The pathophysiology of colorectal cancer, the morphology and physiology of the colon, and the most recent developments in colon-targeted drug delivery systems are the main topics of this review. To improve site-specific delivery and get beyond obstacles including pH fluctuation, enzymatic degradation, and restricted permeability, a variety of nanocarriers have been developed, including liposomes, hydrogels, microspheres, and polymeric nanoparticles. Techniques such as time-dependent, redox-responsive, pH-sensitive, and microflora-activated systems are covered. Additionally, a summary is provided of recent developments in immunotherapy, targeted therapy, and formulations based on nanomedicine for the treatment of colon cancer. Notwithstanding notable advancements, issues with stability, biocompatibility, large-scale manufacture, and regulatory approval still exist. Further investigation into surface modification, combination medicines, and nanocarrier design could transform colon cancer treatment and enhance patient outcomes.

Keywords: Colon cancer, Nanotechnology, Targeted drug delivery, Liposomes, Nanocarriers, Controlled release, Immunotherapy.

Introduction

Recently, a variety of drugs have been administered via drug delivery systems designed specifically for the oral colon. Drugs can be administered orally or rectally to the colon. Rectal dosage forms (enemas and suppositories) are not usually successful due to their extreme unpredictability. Therefore, it is advised to use the oral method.. Traditional oral formulations are absorbed from the stomach and intestine after dissolving there. Achieving a successful colonic drug administration requires overcoming the primary barrier to oral medication delivery, This is the upper gastrointestinal tract's absorption and breakdown of drugs.

(GIT)[1].

Colonic drug distribution may be useful in situations when the colon needs to deliver the medication locally or when the medications are prone to breaking down in the upper gastrointestinal tract environment. Maximum therapeutic benefits will be ensured by drug release at this location. lon as aResearchers have usedOral medication delivery, which achieves a high local concentration while reducing side effects from drug release in the upper gastrointestinal tract or unnecessary systemic absorption, can effectively treat colon diseases like ulcerative colitis, Crohn's disease, carcinomas, and infections. The colon contains a lot of lymphoid tissue, and the colonic mucosa's mast cells absorb antigens and quickly make antibodies locally, which aids in the effective delivery of vaccines. Due to the high residence time and low proteolytic activity, the copotential location for the absorption of peptides, proteins, and vaccines after oral administration is currently receiving a lot of interest.

Targeted systemic absorption in the gut offers exciting possibilities for treating conditions including inflammation, arthritis, and asthma that are impacted by the diurnal cycle.
a range of tactics in Codd's evolution. Redox-potential-based, pressure-based, pH-dependent, time-dependent, and microflora-activated systems are some of these techniques. The luminal pH ileum and the microbial enzymes in the colon, such as pectinase, amylase, dextrose, glycosidase, and AZ reductase, have been used to generate a number of Codd's. [2] A brief summary of commercially available colon-targeting products worldwide is given in Table 1.
This review article's main subjects are: (1) the architecture and physiology of the colon; (2) the colon as a potential site for systemic and local drug delivery; and (3) several oral drug delivery techniques to the colon.

Elements that have encouraged colon-specific drug delivery:

1) The development of new therapeutic agents for the treatment of colonic diseases.
2) The creation of a colon-targeted delivery method to enhance the efficacy of these medications
3) To produce oral delivery system for proteins and peptides[3].

Colorectal cancer

Cancerous growths in the colon, rectum, and appendix are examples of large bowel cancer. Colorectal cancers originate from adenomatous polyps in the colon. While the majority of these growths in the shape of mushrooms are benign, some eventually develop into cancer. Localized colon cancer is usually diagnosed by colonoscopy. For invasive tumors contained within the colon wall (TNM stages I and II), surgery is a successful treatment. Up to 73% of them can be cured with chemotherapy and surgery when they reach stage III, or regional lymph nodes, if treatment is not received. Cancer that spreads to remote areas (stage IV) is usually incurable, despite the fact that treatment can increase survival and, in rare cases, surgery and chemotherapy have helped patients achieve a cure. Radiation therapy is used to treat rectal cancer [4].

Symptoms of colon cancer can include

a. A change in bowel habits, such as more frequent diarrhea or constipation.
b. Rectal bleeding or blood in the stool.
c. Ongoing discomfort in the belly area, such as cramps, gas, or pain.
d. A feeling that the bowel does not empty all the way during a bowel movement.
e. Weakness or tiredness.

Risk Factors of Colon Cancer

Several conditions and lifestyle habits can increase the chances of developing colon cancer. Major risk factors include:

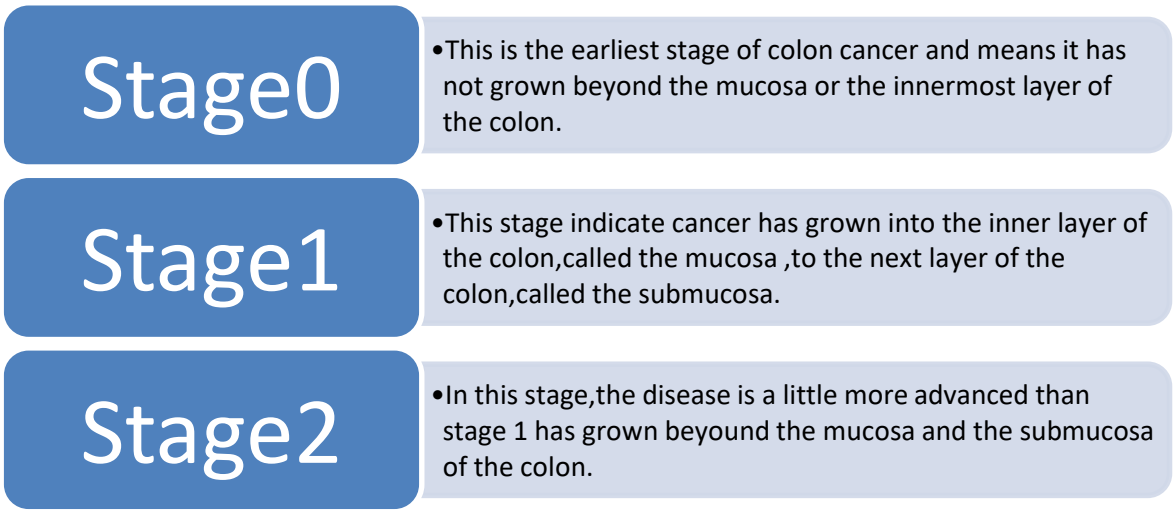
Table 1: Risk Factors of Colon Cancer

Sr no.	Risk Factors	Description
1	Increasing Age	Although colon cancer may occur at any stage of life, it is most commonly seen in people above 50 years.
2	Black Ethnicity	In the United States, Black individuals have a higher likelihood of developing colon cancer compared with other racial groups.

3	Family History	The risk increases if a close blood relative (such as a parent, sibling, or child) has had colon cancer. When multiple family members are affected by colon or rectal cancer, the risk becomes significantly higher.
4	Diet Low in Fiber and High in Fat	A Western-style diet, which typically contains low fibre and high fat, may contribute to colon cancer development. Frequent consumption of processed and red meat is also believed to increase the risk.
5	Diabetes	Individuals with diabetes or insulin resistance are more likely to develop colon cancer than those without these conditions.
6	Obesity	Being overweight or obese raises the risk of colon cancer. Obesity also increases the likelihood of poorer outcomes or death from colon cancer
8	Excessive Alcohol Intake	Heavy drinking can contribute to the development of colon cancer.
9	Radiation Exposure	People who have received radiation therapy to the abdominal region for earlier cancers are at a higher risk of developing colon cancer later in life.

Stages of colon cancer

There are five stages of colon cancer. Three of the four stages have three sub-stages. The colon cancer staging system includes the following:



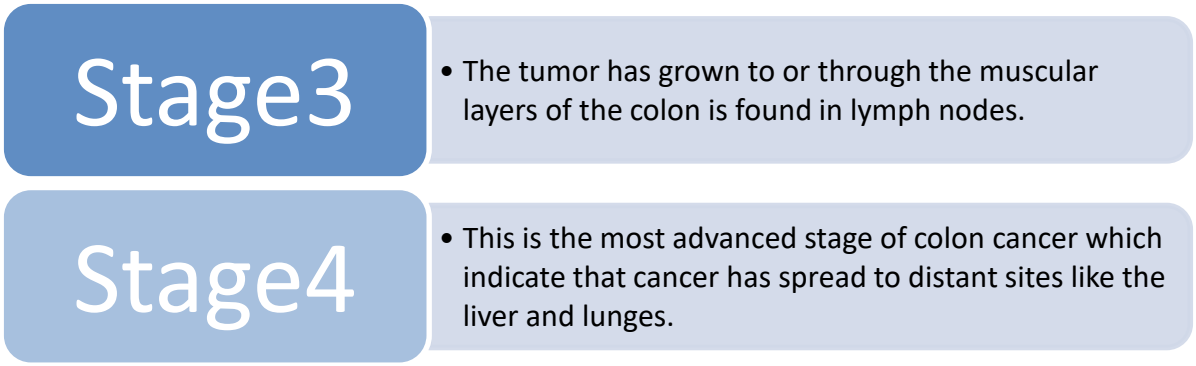


Fig 1: Stages of Colon cancer

Types of colon cancer

Table 2: Types of Colon cancer

Type	Frequency	Origin
Adenocarcinoma	Approx.95%	Glandular epithelium
Carcinoid tumor	Rare	Neuroendocrine cells
GIST	Very rare	Interstitial cells
Lymphoma	Rare	Lymphoid tissue
Sarcoma	Very rare	Connective tissue
Squamous cell carcinoma	Very rare	Squamous cell
Aden squamous	Very rare	Mixed tissue

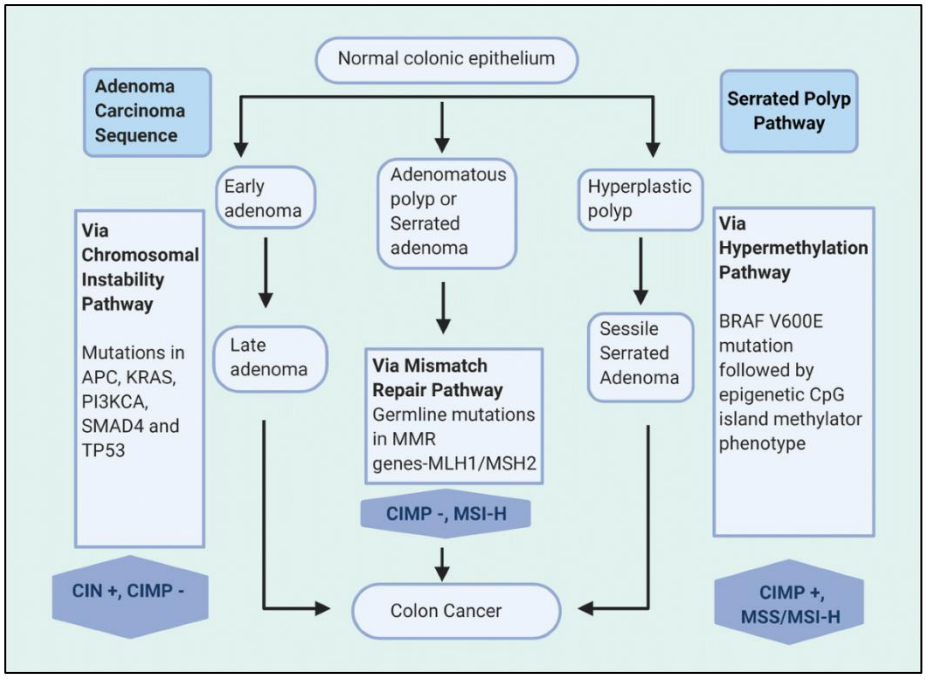


Fig 2: Key molecular pathways in development of colorectal cancer

Drugs used in colon cancer [5]

1) 5-fluorouracil;
2) 9-aminocamptothecin;
3) Capecitabine;
4) Cetuximab;
5) Trino Tecan;
6) Levamisole hydrochloride;
7) Oxaliplatin;
8) Trimetrexate;
9) UFT (forkful and uracil);
10) Bevacizumab;
11) Cisplatin

Advantages of colon targeting drug delivery system: [6-8]

Drug delivery system: The colon is a perfect location to administer drugs to treat local colon disorders.

One benefit of local treatment is that less medication is needed.
decreases the frequency of dosage.

Thus, the price of pricey medications is reduced. perhaps lowering the frequency of drug interactions and adverse effects.

Theocons is a desirable location where medication molecules that are poorly absorbed may have better bioavailability.

Minimize stomach discomfort brought on by certain medications (such as NSAIDs)

First pass metabolism, bye pass.prolonged exercise during the day or at night.Boost patient adherence.

system for targeted drug delivery.It appears to be very responsive to treatments that improve the absorption of poorly absorbed medicines and has a longer retention time [8].

Limitation of colon targeting drug delivery system

- Difficult to access colon.
- Successful delivery requires the drug to be in solution before it arrives in the colon, but the fluid content in the colon is lower and more viscous than in upper GIT, which is the limiting factor for poorly soluble drugs.
- Lower surface area and relative tightness of the tight junctions in the colon can restrict drug transport across the mucosa in to the systemic circulation.[11]
- Non availability of an appropriate dissolution testing method to evaluate the dosage form in-vitro [12].
- An important limitation of the pH sensitive coating technique is the uncertainty of the lo cation and environment in which the coating may start to dissolve. Normal in patients with ulcerative colitis [13,14].

Need for colon targeting drug delivery

Targeted medication delivery to the colon is required to give direct treatment at the illness site (local delivery), at a lower dosage, and with fewer systemic adverse effects [15]. Site-specific or targeted drug delivery methods could be used to administer peptide and protein medications orally; colon-specific formulations could also be used to prolong medication delivery [16]. Colon diseases may be treated with colon-specific drug

delivery systems [16]. The colon can be used for local or systemic drug delivery as well as topical treatment for inflammatory bowel conditions including Crohn's disease or ulcerative colitis. Such inflammatory conditions are usually treated with glucocorticoids and sulfasalazine [17].

Colonic delivery formulations can also be used to administer medications that are polar and/or vulnerable to enzymatic and chemical breakdown in the upper gastrointestinal tract, which is greatly influenced by hepatic metabolism, namely therapeutic proteins, and peptides [18].

Anatomy and Physiology of the Colon: [19,20]

From the end of the ileum to the anus, the large intestine extends. The large intestine in humans is around 1.5 meters long (Table 1). The colon is mostly found in the belly and makes up the top five feet of the large intestine. The lumen, which has a diameter of roughly two to three inches, is the internal passageway of this cylindrical structure, which is coated with a moist, soft pink tissue called mucosa. The transverse colon, descending colon, sigmoid colon, rectum, and anal canal come after the cecum, which is the first part of the colon and leads into the right colon or ascending colon, which is situated directly below the liver (Figure 2).

The physiological characteristics of the proximal and distal colon vary in several ways that influence the overall function. Regarding drug absorption at various locations. The physical characteristics of the luminal contents in the colon also transform, shifting from liquid in the cecum to semisolid in the distal colon.

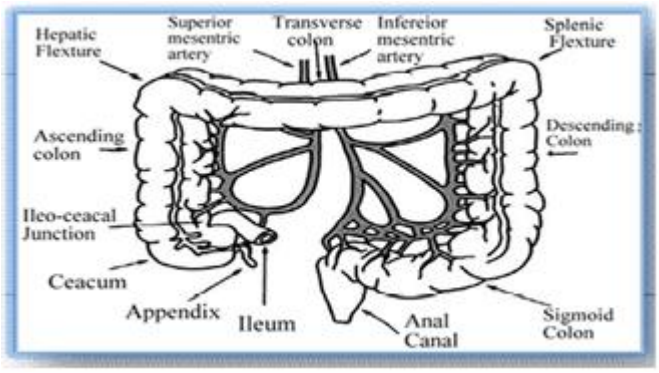


Fig 3: Anatomy of the colon. [21]

pH in the Colon: The gastrointestinal tract's pH level varies both within and across subjects. The pH of the gastrointestinal fluids is greatly influenced by variables such food consumption, diet, and medical disorders. Targeted drug delivery to the colon 9 has been achieved by taking advantage of the pH fluctuations throughout the gastrointestinal tract. The gastrointestinal tract has a pH gradient; the stomach has a pH of 1.2, the proximal small intestine has a pH of 6.6, and the distal small intestine has a pH of roughly 7.5 (Table 1). The presence of short-chain fatty acids, which are created when bacteria ferment polysaccharides, causes the pH to drop when it enters the colon.

Transit of Material in the Colon: The size and density of the dose form, as well as the subject's condition of feeding or fasting, are the main factors influencing the significant variations in the stomach emptying of dosage forms. The rate of stomach emptying and the transit time through the small intestine determine when an oral dose form reaches the colon. Table 2 lists the gastrointestinal tract transit durations for minor oral dose forms.

TABLE 3: OVERVIEW OF ANATOMICAL AND PHYSIOLOGICAL CHARACTERISTICS OF SMALL INTESTINE AND COLON

Region of Gastrointestinal Tract		Length (cm)	pH	Internal diameter (cm)
Stomach	Fundus	2-3	1.5-3 (fasted),	4-5
	pylorus	1.3-1.6	2-5 (fed)	1.5
Small intestine	Duodenum	20-30	6.1(fasted) 5.4(fed)	3-4
	Jejunum	150-200	5.4	4
	Ileum	200-350	7-8	1.8-2.5
Large intestine	Cecum Sigmoid colon	6-7	5.5-7	6
	Ascending colon	20	5.4-5.9	6
	Transverse colon	45	6.1-6.4	5
	Descending colon	30	6.1-7.5	6
	Sigmoid colon	40	6.4-8.0	4-5
	Rectum	12	7-8	4
	Anal canal	3	6.7	2.5-4

TABLE 4: TRANSIT TIME OF DOSAGE FORM IN THE GASTROINTESTINAL TRACT

Organ	Transit time (hr.)
Stomach	<1(Fasting)>3(Fed)
Small intestine	3-4

A number of factors, including as food, dietary fiber content, physical activity, stress, sickness, and drugs, can affect the slow and variable transit of materials through the colon. Dosage forms like capsules and tablets normally pass through the colon in 20–30 hours in healthy young and adult males, though it can take anything from a few hours to more than two days. Drug distribution is significantly impacted by conditions that affect intestinal transit: constipation reduces colonic transit, whilst diarrhea increases it. However, the transit time appears to stay rather consistent in the majority of illness conditions.

Colonic Micro Flora and their enzymes: Intestinal enzymes are utilized to initiate drug release in various sections of the gastrointestinal tract (GIT). Generally, these enzymes are derived from gut microflora, which are present in large numbers in the colon. These enzymes function to dismantle coatings or matrices and to sever bonds between an inert carrier and an active agent (i.e., facilitating the release of a drug from a prodrug). Twenty to thirty percent of the more than 400 different bacterial species that have been identified are members of the genus Bacteroides. Gram-positive facultative bacteria make up the majority of the very few bacteria found in the upper portion of the gastrointestinal tract.

The human colon contains between 10-11 and 10-12 CFU/ml of bacteria. Bacteroides, Bifidobacterium, Eubacterium, Pepto streptococcus, Pepto coccus, Ruminococcin, and Clostridium are the most important anaerobic bacteria. Table 3 summarizes the major metabolic processes carried out by gut microorganisms.

TABLE 5: ENZYMES IN THE COLON THAT METABOLIZE DRUGS AND CATALYZE REACTIONS

Enzymes	Microorganism	Metabolic reaction catalyzed
Nitro reductase	E. coli, Bacteroides	Reduction of aromatic and heterocyclic nitro compounds
Az reductase	Clostridia's, Lactobacilli, E. coli	Reductive breakdown of azo compound
Esterase and amides	E. coli, Voulgaris, B. subtilis, Myoids	Breakdown of esters or amidases of carboxylic acids
Glycosidase	Clostridia, Eubacterium	Breakdown of β-glycosidase of alcohols and phenol
Glucuronidase	E. coli, A. aerogene	Breakdown of β-glucuronidases of alcohols and phenols

Functions of Colon

1. An environment and location that are ideal for the growth of colonic microorganisms

A. The cytochrome content of these bacteria is extremely high. The large intestine's natural flora has a beneficial function and inhibits the growth of other harmful bacteria.

B. Cellulose can be broken down by certain bacteria. Constipated individuals have been found to be more capable of breaking down cellulose than normal persons, which reduces the bulk [22].

2. Stool formation and face contents storage reservoir.

3. Water and potassium are absorbed from the lumen, creating facial content. Here, amino acids, glucose, saline, and certain anesthetics are better absorbed.

4. Excretion and secretion of mercury, arsenic, bismuth, potassium and bicarbonate, etc.

5. Synthesis function: The colon's microorganisms produce folic acid and vitamin K.

Criteria for Selection of Drug for CDDS

Drugs that are poorly absorbed in the stomach and small intestine, including peptide-based medicines, are most suited for colon-targeted drug delivery systems (CDDS). Local colon administration is a great option for medications used to treat colon cancer, diarrhea, ulcerative colitis, and IBD [23]. Table [24–26] summarizes the selection criteria for CDDS medications.

Table 6: Criteria for Selection of Drug for CDDS

Criteria	Pharmacological class	Non-peptide drugs	Peptide drugs
Drugs used for local effects in colon against GIT diseases	Anti-inflammatory drugs	Oxprenolol, Metoprolol, Nifedipine	Amylin, Antisense oligonucleotide

Drugs poorly absorbed from upper GIT	Antihypertensive and antianginal drugs	Ibuprofen, Isosorbides, Theophylline	Cyclosporine, Desmopressin
Drugs for colon cancer	Antineoplastic drugs	Pseudoephedrine	Epoetin, Glucagon
Drugs that degrade in stomach and small intestine	Peptides and proteins	Brompheniramine, 5-Flourouracil, Doxorubicin	Gonadorelin, Insulin, Interferons
Drugs that undergo extensive first pass metabolism	Nitroglycerin and corticosteroids	Bleomycin, Nicotine	Protirelin, semolina, Serotonin
Drugs for targeting	Antiarthritic and anathematic drugs	Prednisolone, hydrocortisone, 5-Amino-salicylic acid	Somatropin, Urodilatin

CDDS is also influenced by the drug carrier.

The physiochemical makeup of the drug and the ailment for which the system is intended determine which carrier is best for a certain medication. The carrier selection is influenced by elements such the drug's chemical makeup, stability, and partition coefficient as well as the kind of absorption enhancer selected. Furthermore, the functional groups of the drug molecule influence the choice of drug carrier [27] for instance, a drug's nitro or aniline groups can be utilized to form an azo bond with another benzene group. The systems' efficacy and release characteristics may be impacted by the carriers, which include additives such hydrogels, coating agents, and polymers (which can be utilized as matrices.[23]

Factors Affecting Performance of the Oral Colon Drug Delivery System

The oral Codd's performance is influenced by several factors. After making it through the stomach and small intestine, the medication delivery mechanism must get in the colon undamaged. The gastrointestinal pH, gastrointestinal transit time, stomach emptying, colonic microbiota, and colonic absorption are the main determinants of the Codd's and are covered in brief below.

1) Gastrointestinal pH:

The effectiveness of the oral Codd's is significantly impacted by the pH of the entire GIT. The GIT's pH fluctuates greatly and is influenced by both and differences within the same subject. Food consumption, illness, and diet all affect the gastrointestinal fluid's ph. Table 5 lists the pH values of the different GIT areas. The pH gradient is not in ascending order, which should also be mentioned. When designing Codd's, this pH shift along the GIT is a key factor[28]. This can be accomplished by employing pH-sensitive coatings, which disintegrate at neutral pH but remain intact at low stomach ph. The small intestine releases drugs prematurely, according to in vitro testing of pH-dependent systems[29]

The ileum and colon have very little pH difference, hence designing Codd's using pH-dependent polymers requires careful formulations[30]

2) Gastrointestinal Transit Time:

Oral drug distribution to the colon is dependent on small bowel transit duration and gastric emptying. The two states of being fed and fasting have a significant impact on the intestinal transit time. Drugs used while fasting leave the stomach in an hour, whereas those taken while feeding can take up to ten hours [31]. Regardless of variables like physical condition, the availability of food, and dosage form size, the small intestine transit time is comparatively constant, spanning between 3 and 4 hours. Furthermore, several variables, including the quantity of the dose forms, the presence of meals, gender, illness, and stress, affect colonic transit time [32-37].

Stress also shortens the transit time of the colon. Drugs that act on the parasympathetic or sympathetic neural systems have been demonstrated by Haeberlin and Friend [38] to alter propulsive motor activity, which in turn affects colonic transit time. Additionally, patients with diarrhea had shorter transit times, while those with constipation have longer transit times.[39]

TABLE 7: pH of Various Regions of the GI [40-41]

Region	pH
Stomach	
- Fasted state pH	1.5–2
- Fed state pH	2 -6
-Small intestine Colon	6.6 to 7.5
- Ascending colon (right colon)	6.4
- Transverse colon (mid-colon)	6.6
- Descending colon (left colon)	7.0

3) Gastric Emptying Rate

The rate of gastric emptying significantly affects the entry of the oral dosage form in the colon; the size of the particles and the fed state determine the residence time of the particles in the stomach; the caloric content of the food affects the rate of gastric emptying; females have a significantly lower rate of gastric emptying than males; stress accelerates the rate of gastric emptying while depression slows it down; high caloric value, acidity, and osmolarity, as well as the size and type of dosage form. The size of the meal, solutions, and little pellets (2 to 3) all affect the retention duration of the large single-unit dosage form, which is longer.

. While the retention time of the large single-unit dosage form is longer and influenced by the size of the meal, solutions and small pellets (2 to 7 mm in size) have been reported to be emptied from the stomach quickly [42,43] and were unaffected by the individual's digestive state.

4) Colonic Absorption:

Absorption of drug through colon follow both paracellular and transcellular routes.

- Paracellular route

Here the drug molecule absorbs through the colonocytes.
Lipophilic drug absorbs through this route.

- Transcellular route

Here drug molecule transport through the tight junction between the colonocytes.
Hydrophilic drug absorbs through this route.

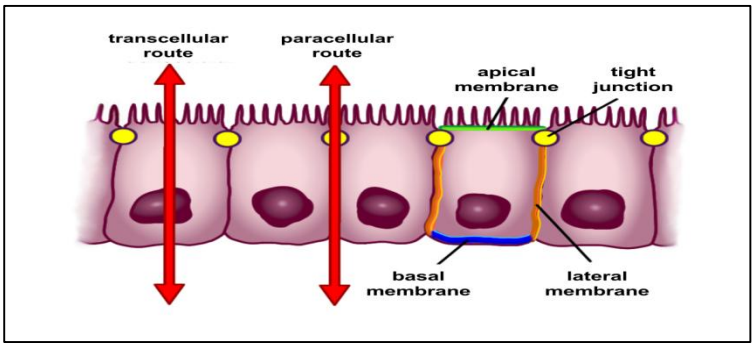


Fig 4: Paracellular and Transcellular route

Drug which well absorbed: glipalamide, diclofenac, theophylline, ibuprofen, metoprolol and oxprenolol.
Drug which poorly absorbed: *furosemide, piretanide, bulimulid,* atenolol [44]

Factor affecting drug absorption

1)Physiochemical properties of drug

a. ***Drug solubility and dissolution rate:*** The rate-determining step and the rate of drug penetration for the absorption of hydrophobic drugs, including griseofulvin, are the drug's dissolution in spironolactone.

b. ***Particle size and effective surface area:***

The relationship between particle size and surface area is inverse; that is, the smaller the particle, the larger its surface area. Surface area comes in two varieties. The whole area of a solid particle is known as its "absolute surface area," and the area of a solid surface that is truly exposed to dissolving media is known as its "effective surface area." It is evident from the Noyes Whitney theory of dissolution that solid particles with a higher surface area dissolve more quickly.

c. ***Polymorphism:***

Polymorphism is the phenomenon of crystals existing in multiple crystalline forms that differ from one another in terms of their physical characteristics, such as solubility, melting point, density, hardness, and compression. Since the stable form of the polymorph has the highest melting point and the lowest energy state, it is less soluble in water.

Because the meta stable form has the lowest melting point and the greatest energy state, it is more soluble in water and has a higher bioavailability. Since the amorphous form has the greatest energy state, it is more soluble in water than the crystalline form:

Amorphous> Metastable > Stable

d. ***Pseudo polymorph:***

Solvate is the term for a solid when solvent molecules are incorporated into the crystal lattice; it can exist in various crystalline forms known as pseudo polymorphs; when the solvent is water, the solvate is referred to as a hydrate. Because hydrate is already associated with water, it requires less energy for crystals to shatter, making anhydrous forms of drugs more soluble in water.

e. ***Drug lipophilicity:***

Lipophilic drug better absorb than hydrophilic drug.

f. ***Drug stability:***

Drugs that degrade into inactivated state or combine with excipients to produce complexes that are poorly absorbed from the GI are the two main causes of low bioavailability.

2) Patient related factors

a. ***Age***

Compared to senior patients, who have low stomach pH and intestinal surface area, infants have high stomach pH and intestinal surface area, and their poor blood flow to the GI causes impaired absorption.

b. ***Gastric emptying time***

Passage of food from stomach to the small intestine is called gastric emptying. Several factors which effect gastric emptying time are following:

- ***Meal volume:*** Larger the bulk of meal longer the gastric emptying times.
- ***Composition of meal:*** Fatty meal delayed gastric emptying time
- ***Body posture:*** Lying right side favored gastric emptying time.
- ***Emotional state:*** Stress and anxiety promote gastric motility whereas depression retard it.

c. ***Drug:***

Antacids, anticholinergic, narcotic analgesic, retard gastric emptying whereas metoclopramide, domperidone promote gastric emptying time.

d. *GI pH:*

There is different in hydrogen ion concentration between the stomach and colonic fluid, which effect absorption of several drugs

Table 8: Effect of drug pKa and GI pH on Drug Absorption [45]

Drug	pKa	Site of absorption
Weak acidic drug	**> 8.0**	Unionized at all pH, absorbed through entire length of GI
Pentobarbital	**8.1**	
Hexobarbital	**8.2**	
Moderately weak acidic	**2.5 to 7.5**	Unionized at gastric pH but ionized at intestinal pH, better absorbed from stomach.
Cloxacillin	**2.7**	
Aspirin	**3.5**	
Stronger acid	**< 2.5**	Ionized at all pH, poorly absorbed from GI Unionized at all pH absorbed through entire length of GI
Disodium cromoglycate	**2.0**	
Very weak base	**< 5.0**	
Oxazepam	**1.7**	
Diazepam	**3.7**	
Moderately weak base	**5 to11.0**	Ionized at gastric pH, relatively unionized at intestinal pH, better absorbed from intestine
Reserpine	**6.6**	
Heroin	**7.8**	
Stronger base	**>11.0**	
Guanethidine	**11.7**	Ionized at all pH, poorly absorbed from GI

❖ Approaches for colon drug targeting:

1. Prodrug approaches

Formation of prodrugs (example: azo-Prodrug, glucuronide conjugate, etc. A prodrug is an inert medication that does not become active unless the body changes or metabolizes it [46]. When taken orally, the medicine and carrier form a covalent bond that allows it to enter the colon without being absorbed from the upper portion of the GIT. Compared to the stomach and small intestine, the colon has higher activity of certain enzymes that cause medication release.

a) **Azo bond conjugate**

Inflammatory bowel disorders are the main conditions for which sulfasalazine is utilized. It is a 5-Amino Salicylic Acid (5-ASA) prodrug. Figure 2 illustrates how 85% of the oral sulfasalazine dose enters the colon unabsorbed and is transformed into 5-ASA and sulphapyridine by the anaerobic environment [47]. Many studies on sulphapyridine lead to the synthesis of other prodrugs, including baseline, polyalanine, and 4-aminobenzoyl-alanine [48]. Glycosidase is one of the well-known classes of enzymes generated by intestinal bacteria. Azo-aromatic polymer (poly-methyl methacrylate hydroxy Rithy methacrylate: 1:5) was found to be superior to pH-sensitive polymer in the evaluation of a colon-specific formulation of flurbiprofen [49].

b) **Glucuronide conjugate**

The main processes for inactivating and preparing a range of medications for clearance are glucuronide and sulphate conjugation. Lower gastrointestinal tract bacteria secrete glucuronidase, which breaks down a number of medications in the intestine. Glucuronide prodrugs should be better for colon-targeted drug administration since the glucuronidation process releases the active drug and permits its reabsorption [50].

c) **Cyclodextrin conjugates**

In both immediate release and delayed release formulations, hydrophilic and ionizable cyclodextrins can function as powerful drug transporters, but hydrophobic cyclodextrins can slow down the pace at which water is released.

Furthermore, the ability of the drug carrier to transport a medicine to a targeted spot is its most desired feature. Cyclodextrin-containing drug conjugates can be a flexible way to create a novel class of colon-targeting soluble prodrugs [51]. Investigations were conducted on ibuprofen prodrugs of and {-cyclodextrins [52]. Methotrexate prodrugs of and -Cyclodextrins were also synthesized, and the results showed that the main goal was to conceal the ulcerogenic potential of the free drug by employing equivalent doses of the ester and a 12-fold dose of the standard dose of methotrexate [53].

d) Dextran conjugates

The metronidazole dextran ester prodrugs have been made and described. The synthesis of dexamethasone and methyl prednisolone dextran ester prodrugs demonstrated the prodrugs' effectiveness in transporting medications to the colon. A succinate linker was used to covalently attach methyl prednisolone and dexamethasone to the dextran [54].

e) Amino-acid conjugates

Polar groups like NH2 and COOH, which are hydrophilic and found in proteins and their basic units (amino acids), lower the membrane permeability of proteins and amino acids.

Drug molecules have been conjugated to these polar amino acids to create a variety of prodrugs.[55]

f) Glycoside Conjugated prodrug

The enzyme The glycosidases "-D-galactosidase, Arabino furanoses, -D-Xylo pyrenoids, and -D-glucosidase" are produced by a number of human microflora. The brush edge of the colon contains these glycosidase enzymes. Glycosides and aglycon are components of naturally occurring drugs. When these drugs are taken orally and enter the colon, glycosidases react with them to release pharmacologically active aglycon. Glycosides are used as a drug delivery system in the colon because of their hydrophilic properties and poor absorption from the digestive system. This approach targets the glucosides, galactosidase, and cellobioses of dexamethasone, prednisolone, hydrocortisone, and fludrocortisone.

The compound daxamethasone-21-glucoside. Two prodrugs, daxamethasone-21-} -glucoside and prednisolone-21-} -glucoside, as well as the unmodified steroids dexamethasone and prednisolone in rate, were used in the study. It has been observed that whereas unmodified steroids are absorbed in the small intestine, both modified forms of steroids reach the cecum.[56]

G) Protein conjugate

Because proteins contain polar groups like -NH2 and -COOH, which reduce the membrane permeability of different proteins, they are hydrophilic in nature. Various prodrugs have been created by conjugating these polar amino acids for site-specific colon drug delivery.

Study has been carried out for colon specific drug delivery of salicylic acid, study involved oral, intravenous, intercaecal and rectal administration of salicylic acid prodrug conjugate with glycylglycine in rabbit.

After two hours when taken orally, salicylic acid showed up in the blood, and the blood's unmodified salicylic acid glycylglycine conjugate was discovered after an intravenous route, whereas the blood sample's free salicylic acid was discovered after an intercaecal route. The study has demonstrated that interstitial microflora oversees cleaving such conjugations; this idea is helpful for administering medication to the colon.[57]

2.Polymeric approach to deliver intact drug molecule to colon

I. *Based on pH sensitive hydrogel*

Protein and peptide drugs can be administered to colonic locations using hydrogels. Enzymes and acidic commoners can break down the azo aromatic cross-links that make up the hydrogels. In an acidic pH, gels

swell less, protecting the drug from stomach deterioration. When the pH of the surroundings increases or becomes more basic, swelling takes place.This makes enzymes like AZ reductase easily accessible, which eventually leads to drug release [58]. Depending on the pH of the surrounding environment, pH-sensitive polymers contain pendant acidic groups like carboxylic acid and sulfonic acid or basic groups like ammonium salt groups that can either give or take protons. At high pH, poly (acrylic acid) becomes ionized. Hydrogels composed of poly (ethylene glycol) (PEG) grafted onto poly (methacrylic acid) (PMA) exhibit special pH-sensitive characteristics. When the pH is low, the carboxyl groups' acidic protons engage with PEG's ether oxygen through hydrogen bonding, causing the hydrogels to shrink. When PMA's carboxyl groups ionize at high pH, the crosslinking density regulates the outcome. For colon-specific medication administration, hydrogels composed of polyanions (such as PAA) crosslinked with haloaromatic crosslinkers were created. As the hydrogel travels down the digestive tract, an increase in pH causes the carboxylic groups to ionize, which causes swelling that is further controlled by the hydrogel's cross-links. This results in little swelling of such hydrogels in the stomach and, thus, minimal drug release. The colon's microbial flora produces AZ reductase, which breaks down the hydrogels' haloaromatic cross-links.

Table 9: Marketed Hydrogel Based system [59,60]

Drug	**Polymer used**	**Approach used**	**Method of preparation**
Carnidazole	Chitosan	pH sensitive	Degradation by Az reductase
5fluorouracil	Match alkyloxy azobenzene	Degradation by AZ reductase	Polymerization

II. Coating with pH dependent polymers

Since the terminal ileum and colon have a higher pH than any other part of the gastrointestinal tract, dosage forms that dissolve at high pH ranges can be directed there.

The terminal ileum region has a higher pH level than the cecum. The ileocecal junction is frequently where dosage forms are delayed; therefore, it is important to carefully choose the thickness and content of the enteric coat to prevent disintegration until the dosage passes through the ileocecal junction from the terminal ileum into the cecum. Eastacryl, Kolli coat MAE, and polymeric methacrylate are substitutes for eudrilid [61]. Mesalamine-containing delayed-release tablets coated with Eudragit S-100 were investigated. These pills released mesalamine in the terminal ileum and beyond for topical inflammatory action in the colon when they dissolved at a pH of 7 or above. Although site-specific mesalamine administration was successfully achieved by the formulation, there have been reports of coating failing to dissolve [62]. Cellulose and derivatives of acrylic acid are the most often used pH-dependent polymers. For colonic medication distribution, pH-sensitive polymers are used to the drug core.

Disadvantages of this method are:

a) Inconsistency in the polymer's disintegration at the targeted location.

b) Absence of site specificity in pH-dependent systems.

Depending on the degree of GI motility, the polymer may dissolve near the end of the ileum or in the distal part of the colon. [63] (Table 6)

Alginate and chitosan were used in the development and evaluation of pH-dependent theophylline hydrochloride microbeads utilizing the ionotropic gelation process, which was followed by enteric coating with Eudragit S100 [64]. Research focused on the formulation of prednisolone with 1% eudrilid RS PM was conducted, demonstrating 100% drug release [66].

Tablet containing mesalamine were investigated which was coated with two polymers euagaric L100 and eudrilid S100 in combination 1:0, 4:1, 3:2, 1:1, 1:5, and 0:1 [65]. Ondansetron-containing chitosan microspheres were made using the emulsion cross-linking technique.

Eudragit S100 and chitosan polymers are combined in this work. According to analysis regression data, Peppa's model may have been the cause of the drug release [67].

Eudragit S100 and L100 were used to create Mebeverine hydrochloride microspheres, which displayed a biphasic release pattern with non-Fiskian diffusion release over the course of 12 hr. [68]

Table 10: pH of Polymer

Sr. No	**Polymer**	pH
1	Cellulose acetate phthalate (CAP)	5.0
2	Polyvinyl acetate phthalate (PVAP)	5.0
3	Hydroxyl propyl methyl cellulose phthalate (HPMCP)	4.8 – 4.8
4	Cellulose acetate taramellite	4.8
5	Eudragit L-30D	5.6
6	Eudragit FS 30D	6.8
7	Eudragit L 100 – 55	5.5
8	Eudragit L 100	6.0
9	Eudragit S 100	7.0

Table 11: pH Dependent formulation [69,70]

Drug	**Polymer**	**Dosage form**	**Disease**
Teased maleate	Eudragit L100, Eudragit S100	Tablet	IBD
Prednisolone	Eudragit L100, Eudragit FS, Eudragit P4135 F	Tablet	Ulcerative colitis

III. Redox sensitive polymer coating

The redox mediators, flavin mononucleotides and benzyl viologen, function as an electron shunt between the extracellular substrate and the intracellular enzyme, changing the redox potential and inducing bond breaking and drug release from the polymer. This new polymer is broken down by redox mediator-secreting enzymes in a non-enzymatic manner. The redox potential, which is approximately -67±90 mv in the proximal small intestine, -196±97 mv in the distal small intestine, and -145±72 mv in the colon, is altered by colonic microbiota.

. The colon is the target of this idea. NADPH must be present as the electron source for the first substrate believed to be involved in cellular electron transfer for bacterial azo reduction by enzymatically produced reduced flavins to occur under anaerobic conditions. The electron mediator, reduced flavins, which was oxidized by NADPH, serves as an electron shuttle from the NADPH-dependent flavoprotein to the azo molecule.[71]

IV. Embedded in biodegradable polymer matrix

When the tablet coated with polysaccharide reaches the colon, the microflora there (including -Arabino unoxidized, -D-fructosidase, -D galactosidase, -D-glucosidase, and -xyloidine) acts on the polysaccharide, breaking down the tablet matrix and releasing the medication. These polysaccharide base polymers remain

unaffected and resistant to the digestive enzymes present in the upper GI tract. Many polysaccharides, including amylase, guar gum, pectin, chitosan, inulin, cyclodextrins, chondroitin sulphate, dextran's, and locust bean gum, have been studied for use in colon-targeted drug delivery systems. These polysaccharides are cheap, nontoxic, and water soluble; however, they require crosslinking or hydrophobic derivatization to become water soluble. The ideal ratio of hydrophilic and hydrophobic components, as well as the quantity of free hydroxyl groups in polymeric molecules, are crucial [72]. Ibuprofen tablets were made using guar gum and xanthan gum as the matrix former.[73]

V. Timed released systems

(example: pulsatile release, pulsi cap, delayed release, sigmoidal release system)

Its foundation is the idea of stopping the drug's release three to five hours after it enters the small intestine. According to this method, the drug leaves the system after a predefined lag time based on the transit time from the mouth to the colon. The size of the dose form and stomach motility affect the lag time. The Pulsi cap gadget is among the first methods. The non-disintegrating half-capsule body of this device is covered by a water-soluble cap and has a hydrogel plug sealed at the open end. To prevent the issue of variable stomach emptying, an enteric polymer is applied to the entire unit. The hydrogel plug begins to swell once the capsule enters the small intestine and the enteric coating dissolves. To release the contents, the amount of hydrogel is regulated such that it only pops out after the allotted amount of time [74]. In a different method, the medicinal material was combined with organic acids to modify the pH inside the hard gelatin capsule. An ethanolic ethyl cellulose solution was used to seal the capsule's junction. The outermost enteric layer of the coating stops the release of the medicine in the stomach after the capsule has been swallowed.

Following gastric emptying, the enteric and hydrophilic layers dissolve rapidly, allowing water to begin entering the capsule. The acid soluble layer dissolves and the encapsulated medication is rapidly released as the pH of the environment inside the capsule drops due to the dissolution of organic acid [75]. Salbutamol sulfate was developed as part of a chrono modulated medication delivery system to treat nocturnal asthma. The salbutamol sulphate-containing cores were made using the direct compression method with microcrystalline cellulose and sodium bicarbonate as an effervescent agent. They were then successively coated with an outer rupturable layer made of euagaric RL/RS (1:1) and an inner swelling layer made of a hydrocolloid (hydroxypropyl methylcellulose E5) [76]. A drug delivery device that was based on the combination of pH and time sensitivity was examined. Eudragit S100 was applied on top of press-coated mesalamine tablets coated with HPMC E-15 [77]. A new system that depends on pH and time was examined. The system is made up of a core mesalamine tablet that has been compression coated with HPMC K4M (hydroxypropyl methylcellulose). Eudragit L100 is then applied on top of this.

3.Novel Approaches for colon targeting

A. **Osmotic pressure-controlled systems** :The unit travels undamaged to the colon, where the osmotic pressure created by the solvent's entry causes the medicine to be released. Another name for it is OROS. For colon medication delivery, there are two OROS systems.

- **Osment pump**

The interior of this container is connected to the outside world via a delivery hole at one end. Water is allowed to flow through the semi-permeable membrane when the gastric-resistant film dissolves. This raises the pressure inside the device, which causes the inner reservoir to contract and the medication formulation to pump out. It consists of a central impermeable, collapsible reservoir filled with medication and an osmotic layer enclosed by an enteric-coated semi-permeable shell.

- **OROS CT**.

The firm gelatin capsule shell melts right away after consumption. Enteric coating keeps the push and pull unit from absorbing water in the stomach's acidic environment. When the coating dissolves and the medicine

is supplied out of the orifice at a pace regulated by the rate of water transport across the membrane, an osmotic pumping action takes place.[78]

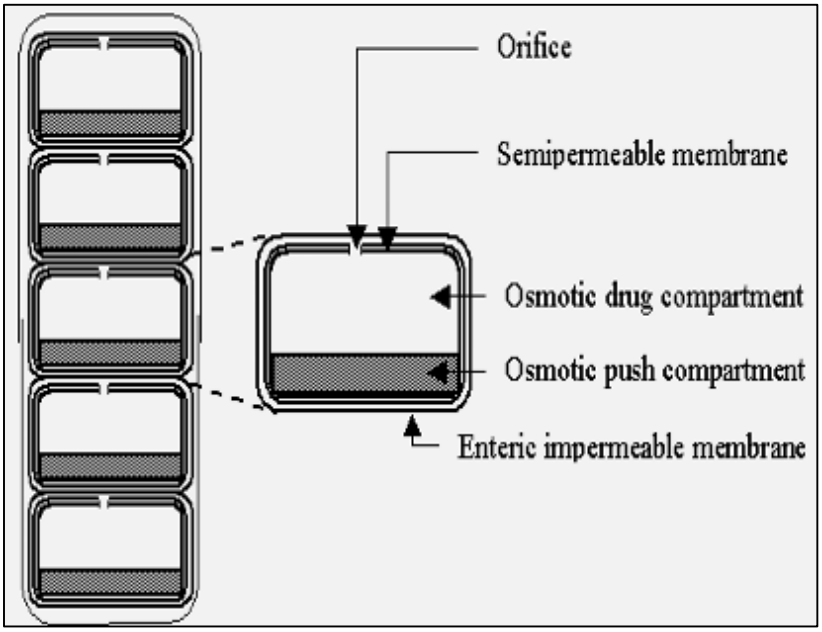


Figure 5: OROS-CT [79]

B. Pulsi cap

made by R.R. Scherer. A capsule consists of a non-disintegrating body component and a water-soluble cover. A water-insoluble hydrophilic hydrogel is used to seal the bodily portion once the medication molecule is inserted. The cap is sealed with enteric polymer once a hole is drilled in it. Because hydrogel is hydrophilic, the capsule dissolves enteric polymer, absorbs water as it passes through the small intestine, and permits intestinal fluid to pass through. After that, it starts to swell and release. The drug release lag time is determined by the length of the hydrogel used.[80]

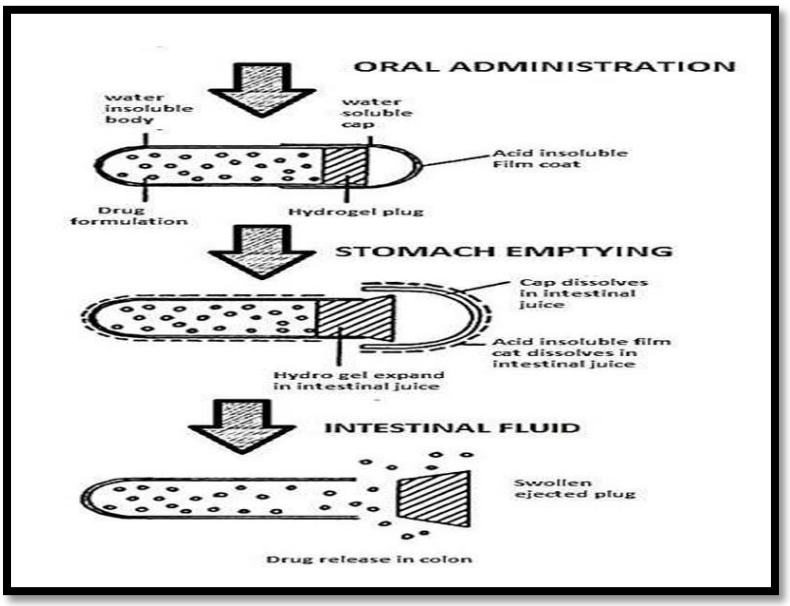


Figure 6: Pulsi cap mechanism of drug release

C. Port system

The Port®, created by Port Systems, LLC, is made up of a hard gelatin capsule covered in a semi-permeable cellulosic membrane. The medication formulation, an osmotically active agent, and an insoluble plug were all present inside the capsule. Water diffuses across the device's semi-permeable membrane upon such contact with the aqueous medium, increasing the interior hydrostatic pressure and eventually ejecting the plug. The coating thickness regulates the lag time. Figure 5 shows the port system's drug release pattern.

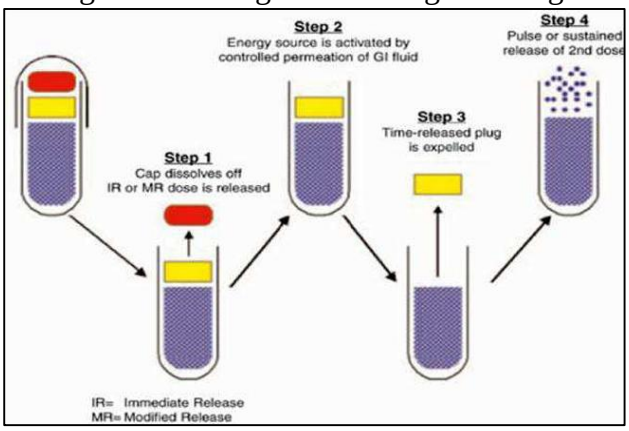


Figure 6: Port system [81]

D. Probiotic approach

Three elements are preferred in this strategy: a triggering temperature, a microbially digested carrier, and a probiotic strain. Bifidobacterium and lactobacillus species are examples of inactive microflora found in probiotic strains. These strains become active at body temperature, begin breaking down the carrier, and release the medication where it is desired. A study employing guar gum as a carrier to assess the in vitro release of diclofenac with or without probiotics discovered that drug release was 54.47% in the absence of probiotics and 73.01% in the presence of them.[82]

E. Gas Empowered Drug Delivery System (GEDD)

Additionally, it is a unique drug delivery method for the colon that uses TMC as a penetration enhancer with CO2 and mucoadhesive polymer polyethylene oxide to target proteins and peptides to the intestinal region. The medicine stays attached to the mucous layer due to the presence of mucoadhesive polymer, and the paracellular pathway for drug absorption is promoted by using a penetration enhancer to open tight junctions. The CO2 gas in this system acts as a driving force to push the medicinal material to the absorbing membrane. It also completely envelops the dosage form to shield it from proteolytic and enzymatic breakdown. Additionally, CO2 improves penetration by mechanically opening the tight connections.[83]

E. Chronotropic system

The foundation of these systems is a drug reservoir encircled by a soluble barrier layer that dissolves over time, followed by the drug's immediate release. Treatment of illnesses impacted by circadian rhythms benefits from such a system. Rheumatoid arthritis, hypertension, and asthma A chronotropic investigation on guar gum crosslinked with ammonium ibuprofen tablets revealed that ammonium inhibits drug release by reducing guar gum swelling.[84]

G. Enteron capsule Technology

Photon research developed It is a round-ended, 32 mm long capsule that holds a medication reservoir that can hold about 1 milliliter. Through a 9 mm diameter opening, the capsule can be filled with a liquid formulation (such as suspension or solution) or a particulate formulation (such as powder, pellets, in-sit effects, etc.). A push-on cover with a silicone O-ring is then inserted to close the capsule. A polymer filament with a high tensile strength holds back the piston face, which serves as the floor of the drug reservoir, against a compressed spring. Using the imaging method of gamma scintigraphy, a radioactive marker is positioned inside a distinct sealed tracer port to provide real-time observation of the capsule location. An externally applied oscillating magnetic field actively ejects the contents of the capsule once it reaches the desired place in the gastrointestinal tract. The magnetic field's frequency is set in the low MHz range, which results in very little absorption in bodily tissue yet is high enough to cause medication release. A tiny heating resistor inside a separate sealed

electronics compartment within the capsule receives the power that the magnetic field induces in the coil. Heat builds up very quickly due to the heater's small size (less than 1mm3).[85]

Table 12: Nanoparticles Based System. [86]

Drug Used	Polymer Used	Method of preparation	Disease
5fluorouracil	Soya lecithin, Dynasan114 and Dyana sin 118	Solid lipid nanoparticles	Colon Cancer
Tripeptide, Lysosomal	Alginate and Chitosan	Double emulsion/Solvent Evaporation	IBD

Table 13: Microsphere Base Colon Targeted System [87,88,89]

Drug Used	Polymer Used	Method of preparation	Disease
Theophylline	Ca–Pectinate, Eudragit S100	Ionotropic gelation Method	Antiasthma tic Activity
Indomethacin	Eudragit L100, Eudragit S100	Solvent evaporation Method	Rheumatoid disorders
Acetogenic	Guar Gum	Emulsification	Rheumatoid arthritis

4.Redox sensitive polymer coating

As mimics of intestinal enzymes' azo bond cleavage, novel polymers that hydrolyze nonenzymatically by enzymatically generated flavins are being investigated for colon targeting[90]. Using the common colonic bacterium Bacteroides fragilis as the test organism, the study investigated the reduction of azo dyes amaranth, Orange II, tartrazine, and a model azo compound, 4,4-dihydroxyazobenzene. The azo compounds were found to be reduced at different rates and that the rate of reduction might be related to the azo compounds' redox potential.

5.Bioadhesive systems

The process by which a dosage form stays in contact with a specific organ for an extended amount of time is called bio adhesion. In the event of poorly absorbable medicines, this extended residence time would result in enhanced absorption characteristics or a high local concentration. The development of colonic medication delivery systems can use this tactic. Numerous polymers have been investigated as components for bio adhesive systems, such as polycarbophils, polyurethanes, and copolymers of polyethylene oxide and polypropylene oxide [91].

6. Liposomes

With a particle size ranging from 30 nm to several micrometers, a liposome is a spherical vesicle made up of one or more bilayers of cholesterol and phospholipids. Because these vesicular systems may encapsulate both hydrophilic and lipophilic bio actives, they are beneficial. While the hydrophobic section of the lipid bilayers intercalates hydrophobic items, the inner aqueous portion of liposomes is well covered by lipid bilayers and can entrap hydrophilic entities. They resemble the membranes of actual cells. Their exceptional entrapment efficiency, safety, and biocompatibility have led to them being studied as drug carriers for a long time. Additionally, the surface of these nanocarriers can be readily altered to offer vesicles unique features by conjugating polymers and ligands.

Furthermore, by targeting liposomes for site-specific delivery to solid tumors, bio actives can be released gradually at tumor sites, raising the concentration of bio actives in the solid tumor in comparison to other tissues [92]. Mannosidase liposomes were created by Xiong et al. (2017) to enhance paclitaxel's therapeutic efficacy in colon cancer animals. Because of their target action on the mannose receptor, the mannosidase liposomes demonstrated a greater tumor inhibition rate and CT26 (colon cancer cells) cell uptake [93].

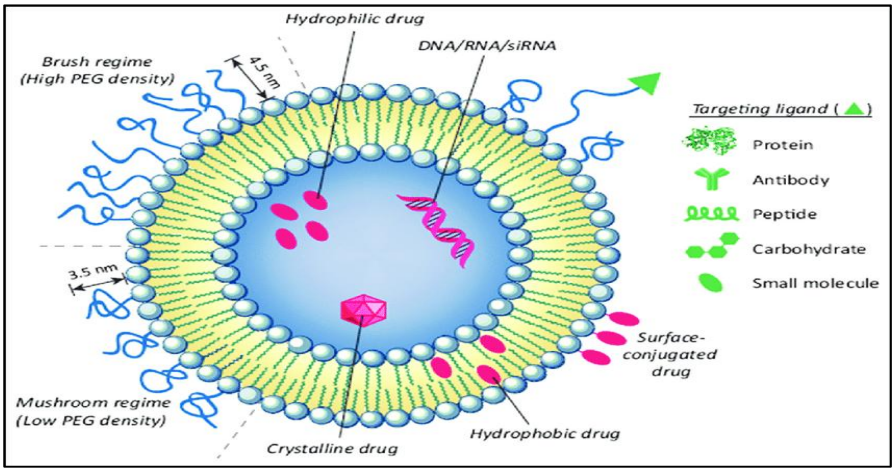


Figure No 7: Liposome

Salmonella-loaded temperature-sensitive liposomes (thrombus) and ultrasound were used to treat colon cancer, according to [120Low-temperature-sensitive liposomes (LTSL) attached to membranes within colon cancer cells were actively transported by the thrombus they produced. This results in the release of doxorubicin. Using the known carrier system (42°C–42°C), high intensity focused ultrasound (HIFU) heating simultaneously polarized macrophages to the M1 phenotype.

The created thrombus was shown to be extremely capable of loading LTSL without compromising their viability through biocompatibility analysis. Thermions were shown to exhibit effective intracellular targeting, high doxorubicin accumulation, and increased production of proinflammatory cytokines in C26 murine colon cancer cells, according to in vitro studies. The combination of thermions and HIFU heating (B30 min) improved macrophage polarization to the M1 phenotype and demonstrated therapeutic efficacy in C26 murine colon cancer cells, according to in vivo data. According to an analysis of the data, focused ultrasonic treatments and thermions may enhance colon cancer treatment [94]. The antitumor activity of bortezomib-loaded nano liposomal formulations was assessed in mice harboring C26 colon carcinoma cells [95]. The C26 colon cancer cell line was used to compare the produced formulations' IC50 values with those of free bortezomib. When tested against the C26 colon cancer cell line, the IC50 values for the liposomal formulation and the free drug were found to be 0.05 6 0.001 and 0.0072 6 0.00075, respectively. The liposomal formulation successfully slowed the growth of the tumor and increased the mice's median survival time (MST), according to an in vivo investigation.

Additionally, the results showed that bortezomib's therapeutic potential might be greatly enhanced by the created liposomal formulation. According to [95], this nanocarrier system shows promise as a medication delivery method in clinical settings.

Evaluation of colon targeted drug delivery system

I) In-vitro Assessment

For CDDS, there is no established technique of assessment. as the GIT's in vivo characteristics, such as pH, volume, stirring, bacteria, enzymes, enzyme activity, and extra gourmet ingredients, should be included in the ideal in vitro model. It is difficult to create a notorious in vitro model because these disorders are typically influenced by food and physical stress. For CDDS, the following in vitro models are used:

a. In vitro Dissolution Test: The dissolution processes of controlled-release formulations used for colon-specific drug administration are sometimes complicated, and the USP's dissolution methods are unable to fully mimic the pH, bacterial habitat, and mixing forces present in in vivo environments. CDDS dissolving tests can be carried out using the conventional basket method. Parallel dissolution studies in different buffers can be used to characterize how formulations respond at different pH values.

b. Tests of a colon

solubility of a particular formulation in a variety of media that mimic the pH levels and timeframes that are anticipated to occur at various stages in the digestive system. For example, the media used were pH 1.2 to simulate gastric fluid, pH 6.8 to represent the jejunal region of the small intestine, and pH 7.2 to represent the ileal segment. Enteric-coated CDDS capsules have been investigated using a gradient dissolution research in three buffers. Examine coating and carrier integrity in vitro in settings similar to the stomach and intestines. Drug release tests were carried out in 0.1 N HCl for two hours (mean stomach emptying time) and phosphate buffer for three hours (mean small intestine transit time).

c. In vitro Enzymatic Test: There are two tests for this:

I. Place the carrier drug system in a fermenter with a bacterially appropriate media.

The quantity of medication delivered at various time intervals was determined (Streptococcus fascism or BoatUS).

ii. Drug release studies are conducted using rat, guinea pig, or rabbit cecal samples, or buffer media con training enzymes (enzyme pectinase, dextranase). contents. The rate of polymer carrier degradation directly correlates with the amount of medicine delivered in each amount of time [96,97]

II) *In- vivo evaluation*

Because they mimic the anatomical and physiological circumstances and bacteria of the human gastrointestinal tract, dogs, guinea pigs, rats, and pigs are used to evaluate the CDDS in vivo. The distribution of different enzymes in the gastrointestinal tracts of rats and rabbits is similar to that of humans.

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III) *γ scintigraphy*

γ-scintigraphy is an image modality that allows the non-invasive visualization of the in vivo performance of drug delivery systems under normal physiological conditions. The following details about the performance of a drug delivery system specific to a colon can be obtained through scintigraphy imaging: the position as a function of time, the starting and final system disintegration time and location, the degree of dispersion, the arrival time of the colon, the residency time in the stomach, and the transit time of the small intestine. Technetium-99m-DTPA has been used as a tracing agent in sodium chloride core tablets in human subjects. Compression coated with guar gum acts as a protective coat against the upper gastrointestinal tract environment. It has been noted that the tablet remains intact in the stomach and intestinal pH but is broken down by colonic microflora as it enters the ascending colon, releasing the drug. [98]

IV) Roentgenography

This method uses radio opaque substance in place of a medication like barium sulfate, which is visible through abdominal X-rays taken after oral delivery. By putting the person under a microscope and capturing a series

of X-rays at different times after oral delivery, it can observe movement, location, and the integrity of the doses. [99]

Recent advance treatment: [100-103]

Table 14: Recent advance treatment

Drug Name	Target / Class	Mechanism of Action	Specific Use
5-Fluorouracil (5-FU)	Antimetabolite (Pyrimidine analog)	Inhibits thymidylate synthase → blocks DNA synthesis; gets incorporated into RNA & DNA causing cytotoxicity	Standard drug for colon cancer (used in FOLFOX/FOLFIRI)
5-Fluorouracil (5-FU)	Antimetabolite (Pyrimidine analog)	Inhibits thymidylate synthase → blocks DNA synthesis; gets incorporated into RNA & DNA causing cytotoxicity	Standard drug for colon cancer (used in FOLFOX/FOLFIRI)
Leucovorin (Folinic acid)	Biochemical modulator	Enhances binding of 5-FU to thymidylate synthase, increasing efficacy	Always given with 5-FU
Capecitabine (Xeloda)	Antimetabolite (Prodrug of 5-FU)	Converted in tumor cells to 5-FU → inhibits DNA synthesis	Oral alternative to 5-FU
Irinotecan (Composer)	Topoisomerase I inhibitor	Prevents re-ligation of single-strand breaks during DNA replication → causes DNA damage and apoptosis	Used in metastatic cases (FOLFIRI regimen)
Oxaliplatin (Elastin)	Platinum analog (alkylating-like agent)	Forms DNA crosslinks → inhibits DNA replication and transcription → induces apoptosis	Used in FOLFOX regimen
Trifluridine/Tapetail (Lonsurf)	Antimetabolite + Enzyme inhibitor	Trifluridine incorporates into DNA → dysfunction; Tapetail prevents degradation of trifluridine	For metastatic, previously treated cases

2. Targeted Therapy Drugs

Table 14.1: Targeted Therapy Drugs

Drug Name	Target / Class	Mechanism of Action	Specific Use
Bevacizumab (Avastin)	VEGF-A inhibitor	Binds VEGF-A → inhibits angiogenesis (new blood vessel	Used with chemotherapy for metastatic cases

		formation) → starves tumor of nutrients	
Ramucirumab (Cyramza)	VEGFR-2 inhibitor	Blocks VEGF receptor-2 → inhibits angiogenic signaling	Second-line for metastatic cancer
Ziv-Aflibercept (Zal trap)	VEGF-trap fusion protein	Acts as a decoy receptor for VEGF → blocks VEGF binding to its natural receptors	Metastatic, second-line
Cetuximab (Erbitux)	EGFR inhibitor (chimeric m Ab)	Binds to EGFR → blocks receptor activation → inhibits cell proliferation	For KRAS/NRAS wild-type tumors
Panitumumab (Weetabix)	EGFR inhibitor (fully human m Ab)	Same as cetuximab but less immunogenic	KRAS/NRAS wild-type colorectal cancer
Regorafenib (Siargao)	Mult kinase inhibitor	Inhibits multiple kinases (VEGFR, PDGFR, RAF) → blocks angiogenesis and tumor growth	Used in refractory metastatic cases
Encaenia + Cetuximab	BRAF + EGFR inhibitor	Inhibits BRAF V600E mutation pathway → reduces tumor cell proliferation	For BRAF-mutated colon cancers
Faruqui Ntini (Eluate)	VEGFR 1/2/3 inhibitor	Inhibits angiogenesis by blocking VEGFR signaling	For advanced/metastatic colon cancer

3. Immunotherapy Drugs

Table 14.2: Immunotherapy Drugs

Drug Name	Class / Target	Mechanism of Action	Use
Pembrolizumab (Keytruda)	PD-1 inhibitor	Blocks PD-1 receptor on T-cells → reactivates immune response against tumor cells	MSI-H or dimmer colorectal cancer
Nivolumab (OPDIVO)	PD-1 inhibitor	Same mechanism as pembrolizumab	Used alone or with ipilimumab
Ipilimumab (Yermo)	CTLA-4 inhibitor	Blocks CTLA-4 → enhances T-cell activation and proliferation	Combined with nivolumab for MSI-H or dimmer colon cancer

Conclusion

With major benefits over traditional therapy, nanotechnology has become a game-changer in the diagnosis and treatment of colon cancer. Liposomes, nanoparticles, microspheres, and hydrogels are examples of nanocarrier-based drug delivery systems that allow for the targeted and regulated release of anticancer drugs, enhancing therapeutic efficacy and reducing systemic toxicity. The use of pH-sensitive, enzyme-activated, time-controlled, and redox-responsive systems, among other strategies, has demonstrated significant promise in improving medication stability and site-specific action in the colon. Notwithstanding these developments, several obstacles still exist, such as restricted drug loading capacity, limitations with large-scale manufacture, erratic in vivo behavior, and safety or regulatory issues. Future studies should concentrate on enhancing clinical translation through thorough in-vivo and clinical investigations, merging nanotechnology with gene and immunotherapy, and optimizing biocompatible and biodegradable nanocarriers. With continued innovation and interdisciplinary collaboration, nanotechnology holds immense promise for developing more effective, safe, and patient-friendly colon cancer therapies.

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