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Review on Novel Approaches for Colon Targeting Drug Delivery Systems.

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Abstract: -

In recent year, there has been a growing interest in colon drug delivery system because of their ability to deliver drug directly to the colon. Various conventional method, including PH-dependent system, time-controlled release systems, and microbially triggered systems, have been extensively researched for targeted drug delivery to the colon. However, these systems have their own limitations, such as the fluctuating PH conditions in the colon, lack of specificity for microbial enzyme, and limited capacity for drug loading. To address these limitations, innovative approaches like nanotechnology-based drug delivery system, prodrug approaches, and bioadhesive systems have been devised.

The GIT terminal part known as colon, has emerged as potential site for delivering various novel therapeutic drugs, particularly peptides. Colon targeted drug delivery system (CDDS) shows promise in treating inflammatory bowel diseases such as ulcerative colitis, Crohn's disuse, colon cancer, and amoebiasis through both systemic and topical drug delivery. This article provides comprehensive review of colon diseases, their diagnosis, the anatomy of the colon, factors influencing drug absorption, and different approaches to colon drug delivery. It also discusses current approaches like the port system, probiotic approach, chronotropic system, colal-pred system, Enterion capsule Technology Multiarticulate system, as well as past studies on colon drug delivery, including evaluation method for site-specific drug delivery to colon.

Introduction:

The delivery of drugs specifically to the colon is greatly sought after for the purpose of treating various bowel diseases, including ulcerative colitis, Crohn's disease, amebiasis, colonic cancer, local treatment of colonic pathologies, as well as the systemic administration of protein and peptide drugs [(1).] The colon serves as a location for the administration of both local and systemic drug delivery. The local method of drug delivery presents an opportunity for topical treatment. The efficacy of the treatment could potentially be enhanced by directing the drug substances specifically to the site of action in the colon [(2).] The field of colonic drug delivery is currently undergoing a resurgence as a result of the numerous pharmaceutical advantages and opportunities that have been uncovered in recent times. By specifically targeting drugs to the colon, it becomes possible to enhance the treatment of localized diseases, gain access to local therapeutic targets, reduce systemic drug exposure and the resulting toxicity, and even enhance drug bioavailability [(3)]

There are several methods or techniques available to achieve colon drug targeting. These include the formation of prodrugs, coating drugs with pH-sensitive polymers, coating drugs with biodegradable polymers, designing formulations using polysaccharides, utilizing timed-release systems, employing pressure-controlled drug delivery systems, and implementing osmotic pressure-controlled systems. Coating drugs with pH-sensitive polymers offers a straightforward approach for delivering drugs specifically to the colon [(4).] Drug which are destroyed by the acid mantle of the stomach and metabolized by pancreatic enzymes are minimally effective in the colon. Sustained colonic release of drugs can be useful in treatment of certain diseases. Furthermore, the colon is a highly responsive site for absorption of poorly absorbable drugs. The successful delivery of drugs to the colon via the gastrointestinal (GI). tract requires the protection of a drug from being released in the stomach and small

intestine [5]. Several approaches have been developed for targeting colon drug delivery. Most of them utilized following four main properties of the GI tract and colon: -

1)Approximation of transit time of the small intestine.
2)Different physiological conditions in different branches of the GI tract.
3)Specificity of bacteria enzymes localized in the colon.
4)Targeting of carrier to colon utilizing targeting moieties specific to colon [5].

In order for a drug delivery system to be deemed effective and achieve success in pharmacotherapy, it is crucial that the drug remains intact and reaches its intended target site or receptor in a concentration that surpasses the minimum effective requirement. To accomplish this objective, it is imperative to consider the dynamic relationship between four key biopharmaceutical factors, as depicted in Figure.1. These factors encompass the drug itself, the formulation it is prepared in, the chosen route of administration, and the desired response at the target site. The latter factor encompasses both the pharmacokinetics (how the drug is absorbed, distributed, metabolized, and excreted) and the pharmacodynamics (how the drug interacts with the target site to produce a therapeutic effect of the drug [6].

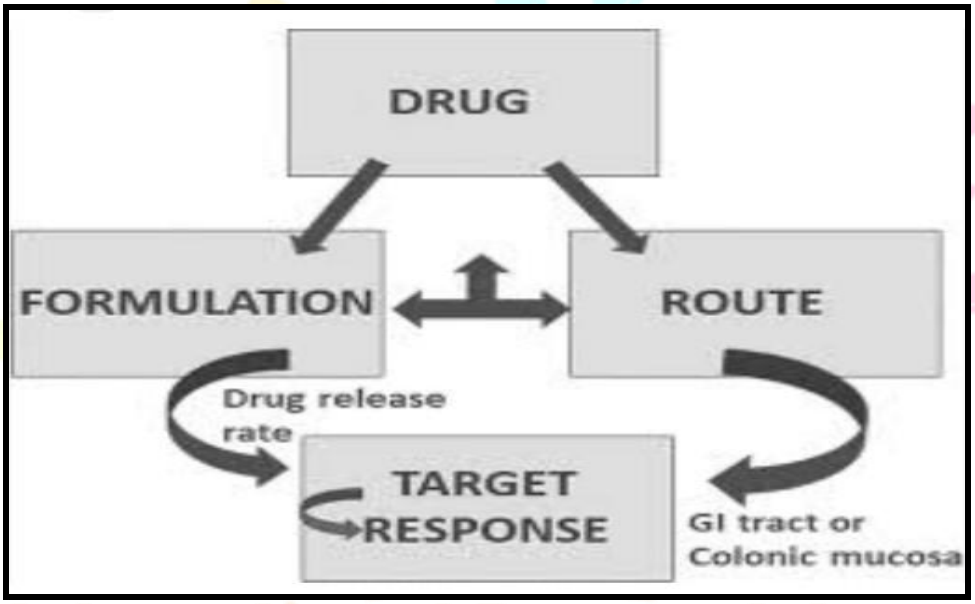

Fig.1- The quartet of rational drug delivery system design.

Anatomy and physiology of colon: -

The gastrointestinal tract is composed of three distinct sections, namely the stomach, small intestine, and large intestine. The large intestine, which spans from the ileocecal junction to the anus, can be further categorized into three primary components: the colon, the rectum, and the anal canal [7]. The entire colon measures approximately 5 feet (150 cm) in length and is comprised of five main segments. These segments are divided by peritoneal folds known as mesentery, which are supported by the ascending and descending colon. The right colon includes the caecum, ascending colon, hepatic flexure, and the right half of the transverse colon. On the other hand, the left colon consists of the left half of the transverse colon, descending colon, splenic flexure, and sigmoid. Finally, the rectum serves as the last anatomical segment before the anus [8]. The human colon is depicted in Figure 1. Its primary function is to establish a conducive environment for the proliferation of colonic microorganisms, serve as a storage reservoir for fecal contents, facilitate the timely expulsion of colon contents, and absorb potassium and water from the lumen. The colon exhibits a remarkably high absorptive capacity, with approximately 2000 ml of fluid entering through the ileocecal valve, of which over 90% is absorbed [4].

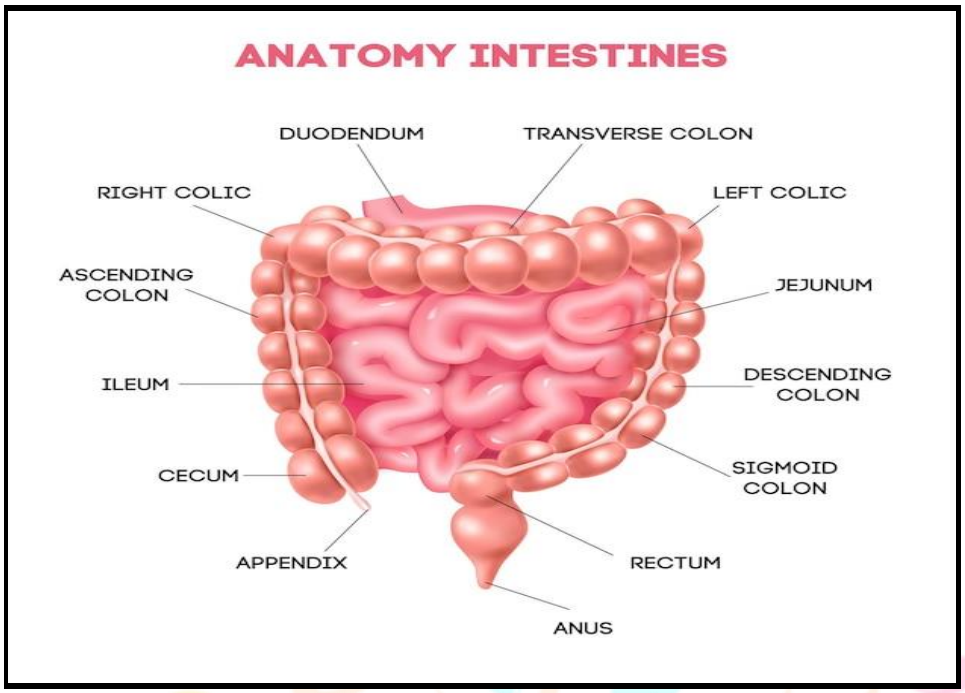

Fig.2-Anatomy of Intestines.

➢ Advantages of Colons Targeting Drug Delivery System: -

- Colon is an optimal location for the administration of therapeutic agents aimed at treating colon-specific diseases. The utilization of local treatment offers the benefit of necessitating smaller quantities of medication [(9).]
- The objective is to mitigate the detrimental consequences associated with the management of colonic ailments, such as ulcerative colitis, colorectal cancer, and Crohn's diseases [(7).]
- The colon presents an appealing location for drug molecules with limited absorption, as it offers the potential for enhanced bioavailability [(4).]
- The system offers the benefit of enhanced therapy, with a lower dosage and decreased occurrence of undesirable side effects commonly associated with higher doses [(10).]
- The drugs used to treat angina, asthma, and rheumatoid arthritis will be released with a delay [(11).]
- Gastric irritation caused by the administration of NSAIDs is effectively prevented [(12).]
- The substantial first-pass metabolism can be limited [(13).]

➢ Disadvantage of colon Targeting Drug Delivery System: -

- The variability of pH levels in the small intestine and colon among individuals can result in the release of drugs at unintended sites. This pH variability may lead to differences in the pattern of drug release from person to person, potentially resulting in ineffective therapy [(14).]
- The challenge lies in the ability to access the colon [(13)]
- For successful delivery, it is imperative that the drug is in a soluble form before reaching the colon. However, the colon has a lower and more viscous fluid content compared to the upper gastrointestinal tract, which poses a challenge for drugs that are poorly soluble [(15).]

➢ Factor affecting on Colon Targeting Drug Delivery System: -

1) Physiological factor.
2) Pharmaceutical factor.

1) Physiological factor: -

a) Gastric emptying

Drug delivery to the colon after oral administration primarily relies on gastric emptying and bowel transit time. The transit time of the dosage form in the colon is contingent upon the particle size, with smaller particles exhibiting longer transit times in comparison to larger particles. Diarrhea patients experience shorter transit times, while constipation patients encounter longer transit times [(4)]. The transit time of various segments within the gastrointestinal tract (GIT) can be categorized into the following parts: fasted state, fed state, small intestine transit, and colon transit. The duration of transit for each segment is as follows: 10 minutes to 2 hours for the fasted state, more than 2 hours for the fed state, 3 to 4 hours for small intestine transit, and 20 to 35 hours for colon transit [(13)]

b) Colon PH

The pH levels of the gastrointestinal tract are influenced by various factors such as diet, disease, and food intake, resulting in both inter and intra subject variations. These pH changes have been utilized for targeted colon drug delivery. Radio telemetry has shown that the highest pH level (7.5 ± 0.5) is found in the terminal ileum, while the pH drops to 6.4 ± 0.6 upon entry into the colon. The mid colon has a pH of 6.6 ± 0.8, and the left colon has a pH of 7.0 ± 0.7. The presence of short chain fatty acids from bacterial fermentation of polysaccharides, such as lactose, causes a drop in pH upon entry into the colon, with lactic acid production resulting in a pH drop to about 5.0[(2).]

C)Colonic microflora and enzyme

A significant quantity of anaerobic and aerobic bacteria can be found throughout the entire length of the human gastrointestinal tract (GIT). Intestinal enzymes are utilized to initiate the release of drugs in different sections of the GIT. Typically, these enzymes are derived from the abundant gut microflora residing in the colon. They serve the purpose of degrading coatings or matrices, as well as breaking bonds between an inert carrier and an active agent, resulting in the release of a drug from a prodrug. More than 400 distinct bacterial species have been discovered, with 20-30% of them belonging to the Bacteroides genus. The concentration of bacteria in the human colon is approximately 1000 CFU/mL. Among the most crucial anaerobic bacteria are Bacteroides, Bifidobacterium, eubacterium, Pepto-coccus, Pepto-streptococcus, ruminococcin, and clostridium [(16).]

d) Drug absorption in colon

The absorption of drugs through the colon occurs via two routes: paracellular and transcellular. In the paracellular route, drug molecules are absorbed through the colonocytes. This route is primarily utilized by lipophilic drugs. On the other hand, in the transcellular route, drug molecules are transported through the tight junction between the colonocytes. This route is mainly utilized by hydrophilic drugs [(11).]

2) Pharmaceutical factor: -

a) Drug carrier

The selection of a carrier for a specific drug candidate is dependent on various factors such as the physiochemical nature of the drug, the disease it is intended to treat, and the type of absorption enhancer chosen. The chemical nature, stability, and partition coefficient of the drug also play a crucial role in determining the carrier selection. Additionally, the functional groups present in the drug molecule, such as aniline or nitro groups, can be

utilized to link it to another benzene group through an Azo bond. The carriers may contain additives like polymers, which can act as matrices, hydro gels, or coating agents, and can influence the release properties and efficacy of the systems [2].

b) Drug candidate

The most appropriate medications for CDDS are those with limited absorption in the stomach and intestines, such as peptides. Local delivery to the colon is an optimal approach for treating IBD, ulcerative colitis, diarrhea, and colon cancer. The selection of a drug carrier is influenced by the specific disease being treated and the physicochemical characteristics of the drug itself. Factors such as the drug's chemical composition, stability, partition coefficient, and absorption enhancers play a role in determining the suitable carrier. Furthermore, the functional groups present in the drug molecule also impact the choice of carrier. The inclusion of additives like polymers, which can serve as matrices or coating agents in the form of hydrogels, can affect the release properties and effectiveness of the systems [17].

- **Approaches for Colon Targeting Drug Delivery System (CDDS): -**

A drug delivery system that targets the colon can be developed using different mechanisms, each with varying levels of efficacy.[18]

1)Primary Approach for CDDS

a) pH-dependent drug delivery to the colon is achieved through the utilization of a polymer coating.
b) The system for controlled release of time.
c) Microbially Triggered.
d)The prodrug approach is employed to facilitate drug delivery specifically to the colon.
e) A methodology based on polysaccharides.

2)Newly Developed Approach for CDDS

a) A system for the controlled delivery of drugs under pressure.
b) A novel system for the targeted delivery of drugs to the colon.
c) osmotic controlled drug delivery.
d) The system of ports
e) Time clock system.
f) Chronotropic system.

1) Primary Approach for CDDS: -

a) pH-dependent drug delivery to the colon is achieved through the utilization of a polymer coating.

The pH of the colon is higher compared to the upper GI tract, making it a suitable target for colonic drug delivery. To achieve this, a drug delivery system is designed using pH-dependent polymers such as cellulose acetate phthalates (CAP), hydroxypropyl methyl-cellulose phthalate (HPMCP) 50 and 55, and copolymers of methacrylic acid and methyl methacrylate. Among various polymers, Eudragit® polymers are widely used for colonic drug delivery due to their mucoadhesive-ness and pH-dependent drug release properties.

The ideal polymer should be able to withstand the low pH of the stomach and the proximal part of the small intestine, but dissolve in the pH of the terminal ileum and the colon. Therefore, drug delivery systems coated with pH-dependent polymers that have a dissolution threshold of pH 6.0–7.0 are expected to delay drug dissolution and prevent premature drug release in the upper GI tract before reaching the colonic sites. However, this pH-dependent system has shown variability in drug release and failure in vivo due to the significant inter- and intra-subject variability in critical parameters such as pH, fluid volumes, GI transit times, and motility [19].

The formulation is shielded in the stomach and proximal part of the small intestine by a polymer that is pH-dependent. However, the polymer may begin to dissolve in the lower part of the small intestine, leading to poor site-specificity of the formulations [18].

Table.1: -Various pH dependent polymers.

Polymer	Threshold pH
Eudragit L 100	6.0
Eudragit S 100	7.0
Eudragit®L-30D	5.6
Eudragit® FS30D	6.8
Hydroxypropyl Methylcellulose phthalate 50	5.2
Hydroxypropyl Methylcellulose phthalate 55	5.4
Cellulose acetate taramellite	4.8

The amount of coating required is generally dependent on the solubility characteristics of the drug, including solubility and dose/solubility ratio. Additionally, the desired release profile, surface area of the formulation, and composition of the coating solution/dispersion also play a role in determining the necessary amount of coating. The coating approach is considered one of the simplest formulation technologies for colon-specific delivery and offers significant advantages in terms of cost and ease of manufacture. From a formulation standpoint, coated dosage forms can be either a single-unit system or a multi-particulate system, and each of these can be a single-layer product or a multi-layer product [(16)]. There is scope for improvement in the field, and the integration of various release-triggering operations in systems can be more effective in treating pathologic deviation than relying solely on pH-dependent systems. Furthermore, the use of nano- and micro-particles shows great promise in targeting specific inflammatory areas in the colon and improving medication absorption [(13)]. The following fig.3 shows the release of drugs.

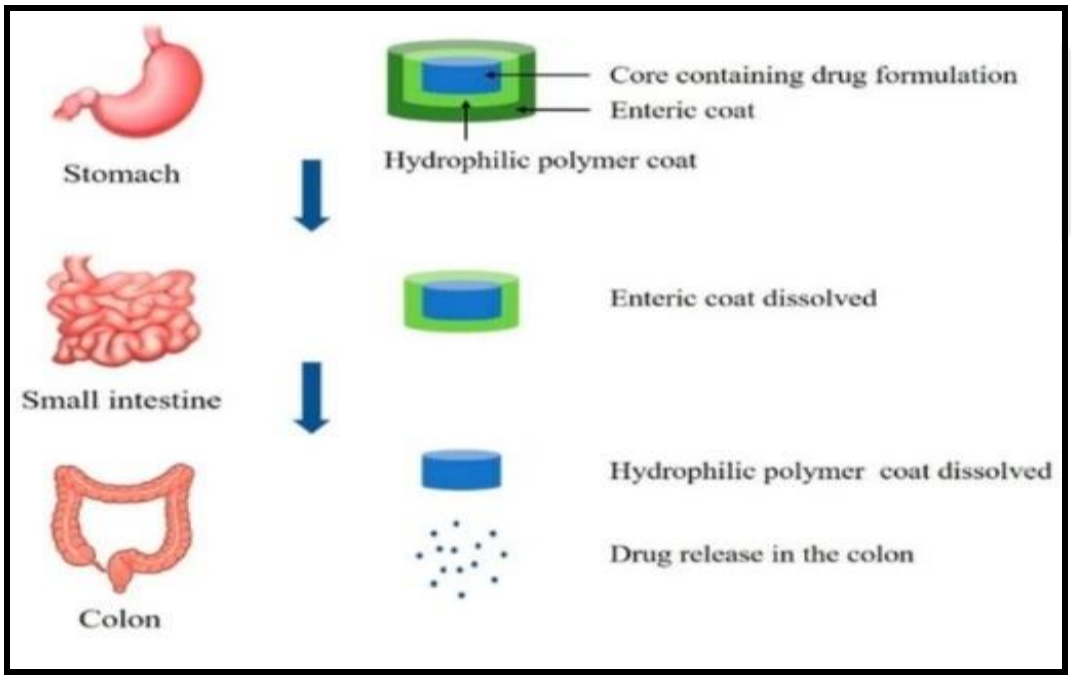

Fig.3: PH dependent DDS.

b) System for controlled release time

Also referred to as pulsatile release, delayed or sigmoidal release system, time-controlled systems are beneficial for the synchronized administration of medication at a predetermined location within the gastrointestinal tract. These systems are especially advantageous in the treatment of diseases that rely on circadian rhythms. Formulations designed for colonic delivery in a time-controlled manner operate on the principle of postponing the release of the drug until it reaches the colon. [18] The primary limitations of this delivery system include the variability in transit time between individuals and the amount of food intake. Additionally, the transit time is influenced by peristalsis or contractions in the gastrointestinal tract. [12]

The transit time of dosage forms through the small intestine typically ranges from 3 to 4 hours. However, similar to gastric emptying, there is significant variability in transit time both between and within individuals. When the stomach is empty, the movement of the small intestine is regulated by repetitive contractions called the migrating motor complex (MMC). In the fed state, contractions within the small intestine occur more frequently and aid in the mixing of luminal contents to enhance enzymatic digestion and nutrient absorption. Consequently, medications pass through the small intestine at a faster rate when the individual is in a fed state. [3]

C)Microbial Triggered System

This approach is one of the most extensively researched topics that has recently attracted the interests of formulation scientists. Natural polysaccharides such as alginate, chitosan, pectin, inulin, and natural gums like xanthan or gellant have been thoroughly explored. The colon, which harbors the highest concentrations of microbial flora in the gastrointestinal tract, contains enzymes that can degrade and break down these natural polysaccharides. Due to the limited presence of microbial flora in the highly acidic environment of the stomach or the alkaline small intestine, dosage forms prepared with such polysaccharides pass through the upper gastrointestinal tract without releasing any drug. However, in the colonic environment, when the enzymes degrade and break down the polysaccharides, drug release occurs. These biodegradable polymers are also safe and nontoxic compared to synthetic polymers used in previous approaches. [20]

Microbially activated systems for drug delivery to the colon are engineered to selectively release drugs in response to the existence of particular microorganisms. These systems hold significant potential for the management of colonic ailments, including inflammatory bowel disease and colon cancer. [21]

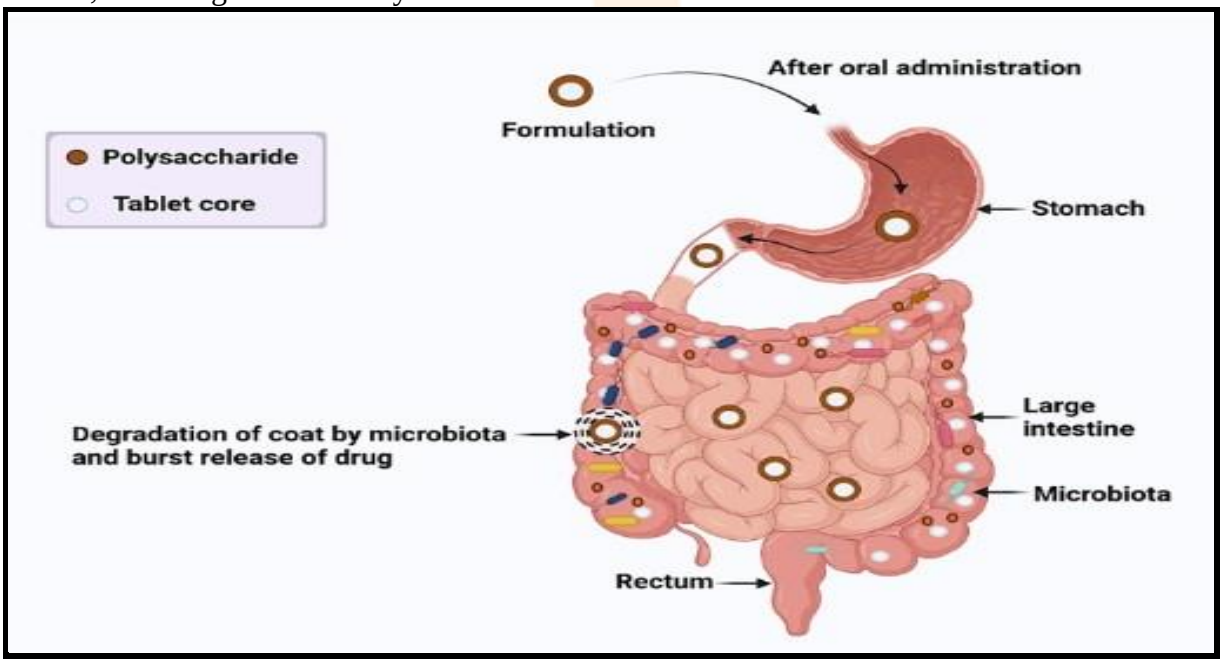

Fig.4: - Microbially Triggered.

d)The prodrug approach is employed to facilitate drug delivery specifically to the colon.

A prodrug is a derivative of a parent drug molecule that is pharmacologically inactive and requires enzymatic or spontaneous transformation in-vivo to release the active components. Prodrugs designed for colonic delivery are formulated to undergo minimal absorption and hydrolysis in the upper gastrointestinal tract and enzymatic hydrolysis in the colon, thereby releasing the active drug moiety from the drug carrier. Intestinal bacteria metabolize azo compounds, which is one of the extensively studied bacterial metabolic processes. Other linkages susceptible to bacterial hydrolysis, especially in the colon, have been developed where the drug is attached to hydrophobic moieties such as amino acids, glucuronic acids, glucose, galactose, cellulose, etc. However, the prodrug approach has limitations as its expression depends on the functional group available on the drug moiety for chemical linkage. Additionally, prodrugs are new chemical entities that require extensive evaluation before being employed as bearers. [22]

Example-

One example of a pro-drug approach for colon drug delivery involves the utilization of mesalamine, a commonly prescribed medication for the management of inflammatory bowel disease. Mesalamine is classified as a pro-drug as it undergoes conversion into its active form through the action of colonic bacteria. Due to its limited absorption in the upper gastrointestinal tract, the pro-drug remains intact until it reaches the colon, where bacterial enzymes facilitate its transformation into the active form.

Azo-Polymeric prodrug-

A polymeric prodrug is formed by sub-synthetic polymers through the incorporation of an azo linkage between the polymer and drug component. The susceptibility of azo polymers to cleavage by the azo-reductase in the large bowel has been observed. [23] Various azo polymers have been assessed as coating materials for drug cores. These polymers have demonstrated a similar vulnerability to cleavage by azo-reductase in the large intestine. The application of polymers cross-linked with azo aromatic groups as coatings for peptide capsules has been discovered to shield drugs from degradation in the stomach and small intestine. Upon reaching the colon, the azo bonds are cleaved by azo-reductase, resulting in the release of the drug. [22]

e) A methodology based on polysaccharides.

Polysaccharides are sugar polymers that are abundant, widely available, affordable, and characterized by a wide range of characteristics and architectures. These can be chemically and biochemically changed and are extremely stable, healthy, non-toxic, hydrophilic, gel-forming, and biodegradable, indicating their usage in oral colon targeting drug delivery system. Numerous polysaccharides, including chitosan, pectin, chondroitin sulfate, dextran's, guar gum, inulin, cyclodextrins, locust bean gum, and amylose, have been evaluated as drug carriers specifically targeting the colon. Various polysaccharides are used for formulating oral colon targeting drug delivery systems. The most promising drug delivery techniques targeting the colon are based on the enzymatic activity of colonic bacteria on polysaccharides. [24]

Table.2-Polysaccharides for colon targeted drug delivery. [18]

Polymers	General properties	Bacterial species that degrade polysaccharide.
Amylose	Unbranched constituents of starch, used as tablet excipients.	Bactericides, Bifidobacterium
Arabinose lactose	Natural pectin, hemicellulose, used as a thickening agent	Bifidobacterium

Chitosan	Deacetylated chitin, used as absorption enhancing agent	Bactericides
Cyclodextrin	Cyclic structure of 6,7 or 8 units used as a solubilizing and absorption enhancing agent	Bactericides
Chondroitin sulphate	Mucopolysaccharides, contain various amounts of esters sulphate at 4 or 6 positions.	Bactericides
Pectin	Partial methyl ester, commonly used as thickening agent	Bifidobacterium, Eubacterium
Dextran	Plasma expanders	Bactericides
Guar gum	Galactomannan, used as thickening agent	Bacteroides, Ruminococcin
Xylan	Abundant hemi cellulose of plant cell wall	Bacteroides, Bifidobacterium

2)Newly Developed Approach for CDDS

a) A system for the controlled delivery of drugs under pressure.

Higher pressures are encountered in the colon compared to the small intestine due to peristalsis. To utilize this colonic luminal pressure for the development of colon-specific drug delivery systems, pressure-controlled colon-delivery capsules have been created using ethyl cellulose, an insoluble polymer in water. These capsules consist of a gelatin coating on the outer side and are filled with the drug. Upon introduction of the drug into the capsule, it dissolves along with a suppository base at body temperature. The water from the intestinal contents is absorbed, resulting in increased viscosity and subsequently increased pressure within the capsule. This increased pressure expels the drug into the colon. [25] The digestive process necessitates the contractile activity of the stomach and peristaltic movements to propel intestinal contents. The gut wall's muscular contraction generates pressure, which is responsible for both grinding and propulsion of the intestinal contents. Throughout the gastrointestinal (GI) tract, the intensity and duration of these contractions vary. Additionally, the colon is recognized for having higher luminal pressure, primarily due to the process involved in stool formation. [23]

b) A novel system for the targeted delivery of drugs to the colon (CODESTM)

The CDDS technology utilized is distinct and effectively addresses issues related to pH or time-dependent systems. It employs a combination of pH-dependent and microbially triggered CDDS, with lactulose serving as a distinctive mechanism for site-specific drug release in the colon. [23] The CODESTM system (depicted in Figure 5) comprises a basic tablet core containing the active ingredient, which is coated with an acid-soluble polymer and a degradable polysaccharide like lactulose. Subsequently, a fresh layer of enteric polymer, Eudragit L 100 or hydroxy methylcellulose (HPMC) polymeric coat, is added, followed by a final coating of Eudragit E polymer. The enteric polymer safeguards the system within the stomach until it reaches the small intestine. In the small intestine's higher pH, the enteric coat begins to dissolve, aided by barrier layers like HPMC or Eudragit L 100, which prevent polymeric coat interactions. In the colon, lactulose dissolves with the help of microflora, producing sufficient acidic media capable of dissolving the acid layer surrounding the drug and affecting the drug dissolution rate. [26]

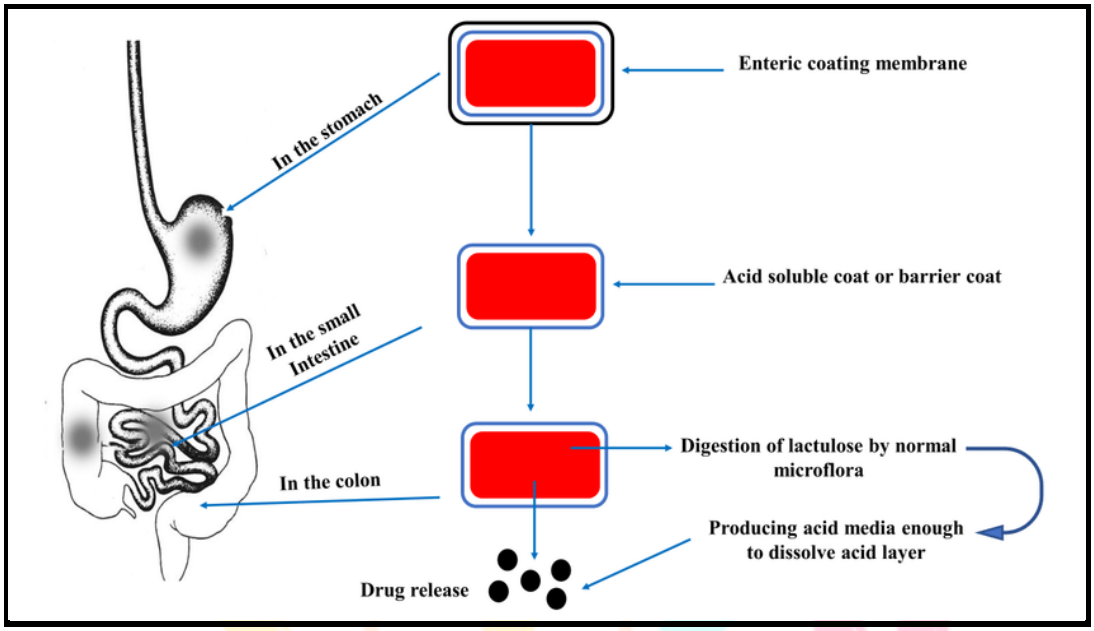

Fig.5-New technology for novel drug delivery systems.

c)Osmotic controlled drug delivery

The osmotic control release oral colon targeting drug delivery systems (OROS-CT). The system developed by Alza Corporation offers a targeted approach for drug delivery in the treatment of various diseases. This system allows for localized drug delivery to the colon or systemic absorption when other methods are not feasible. The OROS-CT system consists of either a single osmotic unit or multiple push-pull units, with the latter incorporating 5-6 units, each measuring 4mm in diameter. These units are encapsulated within a hard gelatin capsule, as depicted in (Figure.6). Each push-pull unit comprises a bilayer structure, consisting of an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. An orifice is strategically drilled through the membrane adjacent to the drug layer. Upon swallowing the OROS-CT system, the gelatin capsule dissolves, allowing the push-pull units to be released. Due to the drug-impermeable enteric coating, the push-pull units do not absorb water in the acidic environment of the stomach, thereby preventing drug delivery at this stage. Once the units reach the small intestine, the enteric coating dissolves in the higher pH environment (pH >7), enabling water to enter the units. This influx of water causes the osmotic push compartment to swell, simultaneously creating a flowable gel in the drug compartment. The swelling of the osmotic push compartment exerts pressure on the drug gel, forcing it out of the orifice. The rate of drug release is precisely controlled by the rate of water transport through the semipermeable membrane. [27]

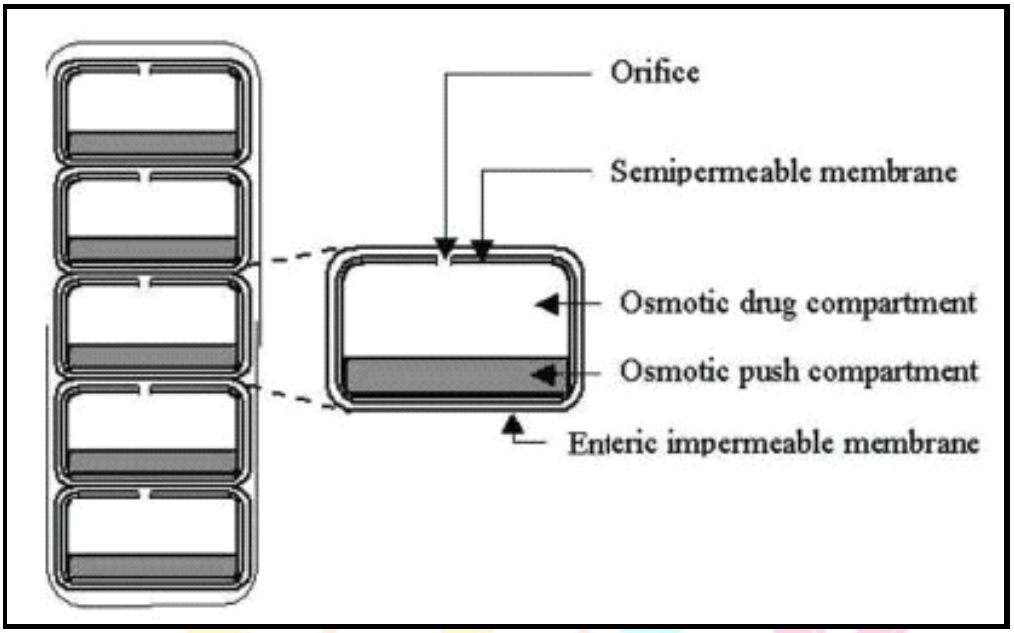

Fig.6- Cross section of the OROS-CT colon targeted drug delivery systems.

d)The system of Ports

The Port® System is composed of a gelatin capsule that is coated with a semipermeable membrane, such as cellulose acetate, and contains an insoluble plug, such as lipidic, as well as osmotically active agents with the drug formulation. When the system comes into contact with an aqueous medium, water diffuses through the semipermeable membrane, resulting in an increased inner pressure that ejects the plug after a certain lag time. The thickness of the coating controls the interim time. This system eliminates the need for a second dose. The pulsatile drug delivery system is based on the principle of delaying drug release until the system reaches the colon, which takes approximately 3-4 hours for the small intestine. A lag-time of 5 hours is typically assumed, which is relatively constant. [(22)] The lag times observed in in-vitro and in-vivo experiments in humans exhibited a strong correlation in the system. This system was utilized for administering methylphenidate to school age children as a treatment for attention deficit hyperactivity disorder. [(18)]

e) Time clock system

In this technique, an aqueous dispersion is utilized for the coating of the solid dosage form. The coating comprises a hydrophobic surfactant layer, to which a water-soluble polymer is incorporated to enhance adhesion to the core. Upon contact with the dissolution fluid, the system undergoes rehydration and redisperses. The control of the lag time in this system is achieved by adjusting the thickness of the coating material in a proportional manner. The impact on the lag time may vary between high-calorie and low-calorie meals, as investigated through gamma scintigraphy. The average lag time for drug release was found to be 5.5 and 5.7 hours, respectively [(28)]

f) Chronotropic system.

An oral drug delivery system can be utilized to target specific diseases, such as IBD. Chronotropic systems, as depicted in Figure 7, are primarily designed to achieve drug release that is time-dependent. Typically, a drug-containing reservoir is coated with a water-soluble polymer, such as HPMC, and the final coat is a gastroprotective polymeric film that is responsible for preventing drug degradation in the stomach. The polymeric film begins to dissolve at higher alkaline pH levels in the small intestine, and the lag time for drug release is dependent on the thickness of the water-soluble coat and the viscosity of the polymer used. [(26)]

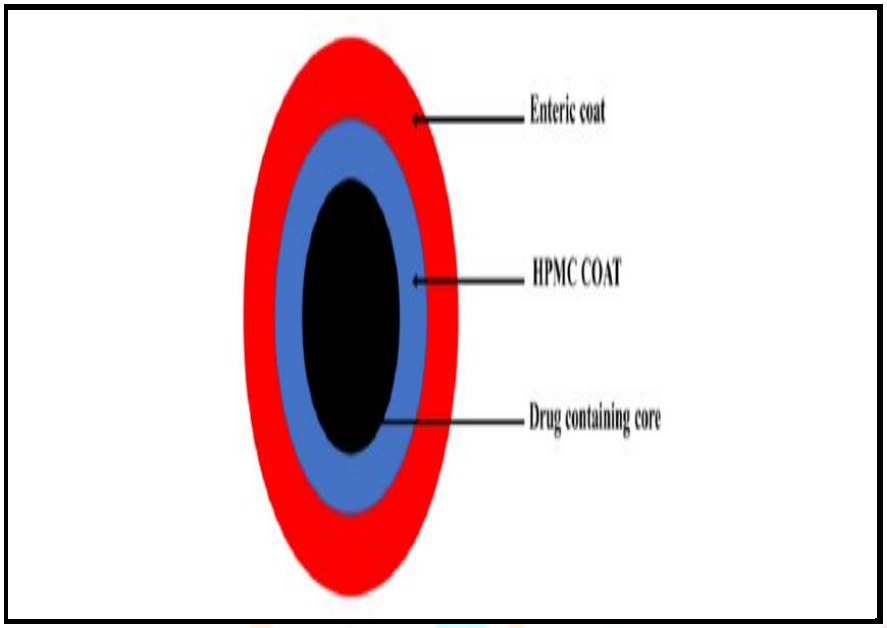

Fig.7-Schematic diagram of chronotropic drug delivery systems

- **Evaluation Parameters of Colon Drug Delivery System: -**

An ideal in vitro model for the evaluation of Controlled Drug Delivery Systems (CDDS) should possess in-vivo conditions of the gastrointestinal tract (GIT) such as pH, volume, stirring, bacteria, enzymes, enzyme activity, and other components of food. However, there is currently no standardized evaluation technique available for in vitro evaluation of CDDS. The conditions required for an ideal in vitro model are influenced by various factors such as diet and physical stress, making it challenging to design a standardized in vitro model. Nonetheless, the following in vitro models are commonly used for the evaluation of CDDS:

a) In vitro dissolution test.
b) In vitro enzymatic test.
c) In vivo evaluation. [22]

a) In vitro dissolution test-

The use of the conventional basket method is applicable for CDDS. Investigation has been conducted on enteric-coated capsules for CDDS in three buffers. The capsules underwent testing for a duration of two hours at pH 1.2, followed by one hour at pH 6.8, and finally at pH 7.4. Dissolution testing of polysaccharide-based colon-specific drug delivery typically involves the incorporation of enzymes, rat caecal contents, and human faecal slurries. [23]

b) In vitro enzymatic test-

The drug delivery device is to be incubated in a fermenter containing bacteria-friendly media, specifically Streptococcus faecium and B. ovatus. The amount of drug released at each time slot is determined through calculation. For drug release studies, a buffer media is utilized, which includes enzymes such as pectinase and dextranase, as well as rat and guinea pig. The rate at which the polymer carrier breaks down is directly correlated to the quantity of medicine delivered within a specific time period. [13]

c)In vivo evaluation-

The in-vivo assessment of the CDDS is conducted in dogs, guinea pigs, rats, and pigs due to their similarity to the anatomical and physiological conditions, as well as the microflora of the human gastrointestinal

tract. The distribution of different enzymes in the gastrointestinal tract of rats and rabbits is comparable to that in humans. [11] Guinea pigs are frequently employed as an experimental model for IBD. The activity of azoreductase and glucuronidase in the gastrointestinal tract of rats and rabbits is quite similar to that in humans. A novel model has been suggested for the prompt assessment of CDDS. In this model, the fetal bowel of humans is transplanted into a subcutaneous tunnel on the back of thymic nude mice. Within a span of four weeks, this transplantation site vascularizes, matures, and gains the ability to develop a mucosal immune system from the host. [22]

Table:3-Techniques Employed in Marketed Drug [34]

Techniques Employed	Polymers used	Drug used
pH dependent	Eudragit L100 and S 100	Mesalazine.
	Eudragit S, Eudragit FS, Eudragit P4135F.	Prednisolone
	Eudragit L 30D55, Eudragit FS 30D	Paracetamol
Time dependent	Hydroxypropyl methyl cellulose	Pseudoephedrine HCL
	Hydroxyethyl cellulose, Ethyl cellulose	Theophylline
	Microcrystalline cellulose, Lactose or Behenic acid	Indomethacin
Bacteria dependent or polysaccharides based	Chitosan	Diclofenac sodium
	Pectin	Indomethacin
	Guar Gum	Dexamethasone

- **Colonic Disease: -**
- Ulcerative Colitis.
- Crohn's Diseases.
- Ischemic Colitis.
- Diversional Colitis.
- Colon cancer.

1)Ulcerative Colitis

Ulcerative colitis is an inflammatory bowel disease (IBD) characterized by chronic inflammation and ulceration of the large intestine's inner lining due to abnormal immune system reactions. Although it can occur at any age, individuals between the ages of 15 and 30 are more susceptible to developing this condition. [29]

1.1) Sign and symptoms-

- Diarrhea.
- Rectal bleeding, characterized by the passage of a small quantity of blood along with stool.
- Abdominal pain and cramping.
- Re frequently accompanied by the presence of blood or pus.
- Rectal pain.
- An urgent need to defecate.
- Weight loss, Fatigue, Fever.
- In children, rectal a failure to thrive. [30]

1.2) Management and Treatment -

Amino-salicylates, including mesalazine and sulfasalazine, immunomodulators like azathioprine, mercaptopurine, and methotrexate, as well as biologics such as infliximab, adalimumab, vedolizumab, golimumab. [31]

2)Crohn's disease-

Crohn's disease, classified as an inflammatory bowel disease (IBD), results in inflammation of the tissues within the digestive tract, leading to swelling.

2.1) Sign and symptoms

Diarrhea, fever, fatigue, abdominal pain and cramping, blood in stool, mouth sores, inflammation of the skin, eyes, and joints, inflammation of the liver or bile ducts, kidney stones, iron deficiency (anemia), and delayed growth or sexual development in children. [32]

2.2) Management and Treatment

The prescription of medicine for individual with Crohn’s disease is contingent upon their specific symptoms. Drug used for their treatment like Aminoglycosides, Corticosteroids, Immunomodulators, Biological therapy. [33]

3)Colonic cancer

The incidence of colon cancer is more common in older adults, but it is not limited to any particular age group. The development of colon cancer usually starts with the formation of polyps, which are small clusters of cells that grow inside the colon. While most polyps are benign, some can eventually transform into cancerous growths.

3.1) Symptoms

Colon cancer symptoms may manifest as alterations in bowel habits, such as increased occurrences of diarrhea or constipation. Additionally, individuals may experience rectal bleeding or observe blood in their stool. Persistent discomfort in the abdominal region, characterized by cramps, gas, or pain, is also a possible symptom. Some individuals may feel that their bowel does not completely empty during a bowel movement. Furthermore, weakness or fatigue may be present, along with unintentional weight loss.

3.2) Prevention

It is advised by doctors that individuals with an average risk of colon cancer should contemplate commencing colon cancer screening at approximately 45 years of age. However, individuals with an elevated risk should consider initiating screening earlier. Those with an elevated risk encompass individuals with a familial background of colon cancer. There exist various tests employed for colon cancer screening. It is recommended to discuss the available options with your healthcare team. [35]

Table-4: Marketed drug product for the treatment of various diseases of the colon. [23]

Sr.no	Marketed Name	Disease	Drug
1)	Mesacol tablet	Ulcerative colitis	Mesalamine
2)	Asacol	Ulcerative colitis, Corh's diseases	Mesalamine
3)	SAZO	Ulcerative colitis, Corh's diseases	Sulphasalazine
4)	Intazid	Ulcerative colitis,	Balsalazide
5)	COLOSP	Irritable colon syndrome	Mebeverine
6)	Cyclominol	Irritable colon syndrome	Dicyclomine

- **Current and future development: -**

There are currently various technologies available for delivering modified release solid formulations to the colon. These technologies utilize factors such as GI pH, transit times, enterobacteria, and luminal pressure to achieve site-specific delivery. Each of these technologies has its own unique design, but they also have certain limitations related to site specificity, toxicity, cost, and ease of scale up/manufacturing. Among these technologies, microbially controlled systems that utilize natural polymers show the most promise for colonic delivery, particularly in terms of site-specificity and safety. One significant technological advancement in this field is the use of a film coating system that combines a polysaccharide with a suitable film forming polymer. However, further advancements in this area are needed to improve the processing of the polymeric blend of polysaccharides and film forming materials, while still maintaining the composition's susceptibility to microbial degradation in the colon [14].

Conclusion: -

Colon-targeted drug delivery systems offer advantages over traditional systemic drug delivery methods. The key benefit of these systems is that the colon provides a longer transit time, a near-neutral pH, reduced enzymatic activity, and increased responsiveness to absorption enhancers. The biggest challenge in colon-specific drug delivery is ensuring that the drug remains intact as it passes through the stomach and approximately six

segments of the small intestine. Researchers have developed various innovative approaches to address this limitation. These include pressure-controlled drug delivery systems, pulsatile systems, reservoir systems, capsules, multiparticulate systems, probiotic approaches, and azo hydrogels. These new approaches are more targeted and specific compared to conventional methods. Both natural and biodegradable polymers are utilized for colon-specific drug delivery. The current demand from the pharmaceutical industry and patient community is to identify the most suitable approach that can safely and effectively deliver medicines in a cost-effective manner, with minimal alteration in terms of the release of drugs at the desired site.

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