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A Review on Concept of Colon-Specific Drug Delivery Systems and Its Evaluation

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ABSTRACT

For the treatment of a range of local diseases, such as ulcerative colitis, Crohn's disease, irritable bowel syndrome, chronic pancreatitis, and colonic cancer colon-specific drug delivery systems (CDDS) are desirable. Also, the colon may be a possible site for many medications to be systemically ingested to cure non-colonic diseases. Drugs such as proteins and peptides that are considered to degrade at intense gastric pH may be systemically ingested by the colonic mucosa if administered to the colon intact. It is important that the delivery system precisely targets the medications in the colon to produce successful therapeutic effects. In the development of colon-targeted drug delivery systems, many formulation methods have been investigated. These methods make the use of components of formulation that associate with one or more elements of gastrointestinal *(*GI*)* physiology, such as the pH discrepancy along the GI tract, the involvement of colonic microflora, and enzymes, to achieve colon targeting. The factors affecting colon-specific drug distribution and colonic bioavailability and the shortcomings associated with CDDS are illustrated in this paper. Also, the analysis includes a comprehensive discussion of different traditional approaches/technologies currently being used for CDDS growth, as well as comparatively newer formulation approaches/technologies.

1. INTRODUCTION:

In recent years, the administration of drugs to the colon has been the focus of many studies because it can improve the treatment of local diseases that affect the colon while minimizing systemic side effects. Medical conditions that affect the colon include ulcerative colitis (UC), Crohn's disease (CD), and irritable bowel syndrome (IBS) [1]. The drugs commonly used to treat these diseases include sulfasalazine, dexamethasone, hydrocortisone, metronidazole, and prednisolone [2]. High concentration drugs can reach the colon with minimal systemic absorption when these drugs are specifically administered to the colon without first being absorbed by the upper gastrointestinal tract [3]. Colon contents have a longer residence time (up to 5 days), and the colon mucosa is known to promote the absorption of certain drugs, making this organ an ideal place for medication administration [3,4]. The drug can be administered to the colon orally or rectally. For convenience, the oral dosage form is the most preferred delivery route for specific colon delivery [4]. The oral assessment form can provide great flexibility in terms of delivery, manufacturing and patient adherence, and relatively safe administration, and they do not require sterile preparation [2]. When targeting specific locations in the colon, direct rectal administration is difficult [2,4].

Also, the extent of drug distribution depends on the rectal dosage form and its diffusion capacity and retention time. The success of the colon-specific drug delivery system (CDDS) depends on the physical and chemical properties of the drug, the type of delivery system, all other factors that can affect gastrointestinal transit time, and the degree of drug-drug interaction of medicines. It depends on the digestive tract [1]. In oral CDDS, the drug must be prevented from being released from the stomach and small intestine [4]. Therefore, the methods used to develop the CDDS aim to delay the release of the drug until the system reaches the colon, and some of these strategies have been more successful than others. Some over-the-counter drug formulations report the combined use of the traditional methods.

Table No. 1: Currently Marketed Formulations

Colon disease/disorder	Drugs	Delivery System
Inflammatory bowel	Mesalazin	
disease	-Asacol®	DR tablets
Ulcerative colitis	-Pentasa®	TR capscules
Crohn's disease	Sulfasalazine(Azulfidine	DR tablets

	EN-tabs®)	
	Prednisone (Rayos®)	Rayos®
	Budesonide	
	- MMX®	Multi-matrix tablets
	- Uceris	ER tablets
	- Clipper	Gastro-resistant prolonged-release tablets
	Prednisolone (Colal-Pred®)	Oral colon-targeted pellets
	Metronidazole (Flagyl® ER)	ER tablets
	Azathioprine (Azasan®)	IR tablets
	Mercaptopurine (Purinethol®)	IR tablets
	Cyclosporine (Gengraf®)	IR capsules, oral solution
Diverticulosis and diverticulitis	Methylcellulose (Citrucel®)	Oral powder, IR tablets
	Psyllium (Metamucil®)	Oral powder, IR capsule
	Mesalazine (Asacol®)	DR tablets
	Rifaximin (Xifaxan®)	IR tablets
Colonic amoebiasis	Doxycycline (Doryx®)	DR tablets
	Metronidazole (Flagyl® ER)	ER tablets
Irritable bowel syndrome	Methylcellulose (Citrucel®)	Oral powder, IR tablets
	Psyllium (Metamucil®)	Oral powder, IR capsules
	Loperamide (Imodium®)	IR capsules
	Dicyclomine (Bentyl®)	IR capsules, IR tablets
	Hyoscyamine (Levbid®)	ER tablets
	Lubiprostone (Amitiza®)	Soft gelatin IR capsule
	Linaclotide (Linzess®)	IR capsules
	Rifaximin (Xifaxan®)	IR tablets
	Amitriptyline (Elavil®)	IR tablets

2. LIMITATIONS OF COLONIC DRUG DELIVERY:

The development of specific drug delivery systems for the colon has been associated with specific limitations and challenges. The main obvious challenge is that the colon is located at the end of the gastrointestinal tract (GIT). An oral dosage form must pass through the

digestive tract to reach the destination. The physiology of the gastrointestinal tract is complex, with a wide range of pH, fluid volume, and transit time. Also, the presence of food and metabolic enzymes increases physiological complexity. These factors prevent reliable and effective delivery of medications to the colon. Another factor is the drug's solubility. Due to the small volume of the colonic luminal fluids, high viscosity, and neutral pH, the solubilization of the drug may be the determinant of the rate of colonic absorption.

Finally, maintaining the stability of the drug in the colon can be a problem. Nonspecific drug interactions with the contents of the colon (such as food waste, intestinal secretions, mucus, or feces) can adversely affect the stability of the drug. Also, bacterial enzymes in the colon can also break down drugs and make them ineffective [5].

3. FACTORS INFLUENCING COLON-SPECIFIC DRUG DELIVERY AND COLONIC BIOAVAILABILITY

3.1 Colonic anatomy

The human digestive tract is mainly divided into the stomach, small intestine, and large intestine intestinal. Their anatomical and physical characteristics are shown in Figure 1. The large intestine extends from the distal end of the ileum to the anus, it is over 1.5 m long and is divided into three parts: colon, rectum, and anal canal. The diameter of the colon is 5 to 7 cm, beginning at the Ileocecal valve to the rectosigmoid colon at the end. The colon itself consists of the cecum, the ascending colon, and the hepatic flexure, transverse colon, splenic flexure, descending colon, and sigmoid colon [6].

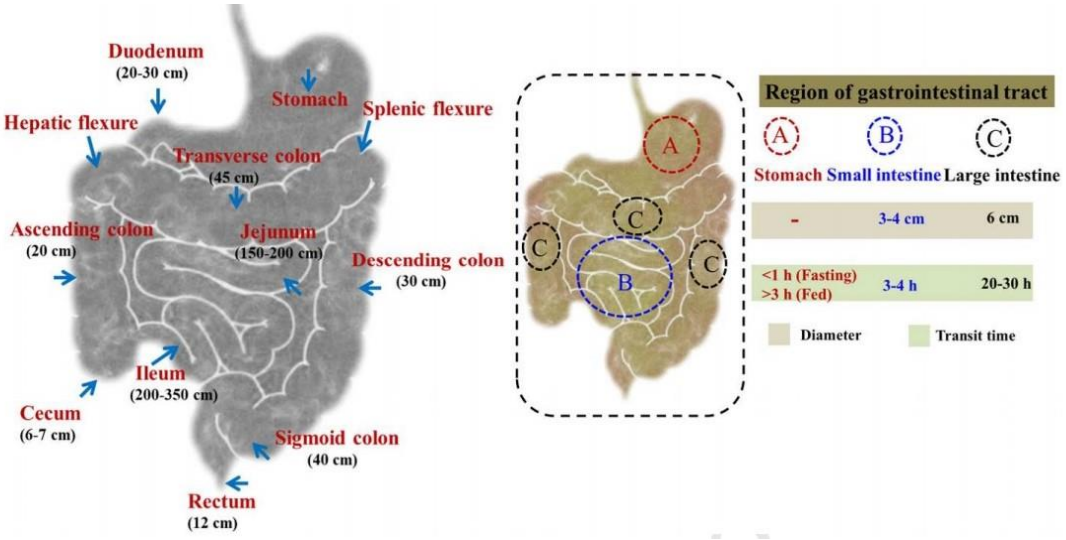

Figure No. 1: **Gastrointestinal Track** [7]

3.2 Colonic pH

The pH value of the gastrointestinal tract varies from region to region and can be used as a method to build a targeted colonic delivery system. The upper gastrointestinal tract has a pH gradient ranging from pH 1.2 in the stomach to pH 6.6 in the proximal small intestine and pH 7.5 in the distal small intestine, respectively. Second, the presence of short-chain fatty acids produced by polysaccharide fermentation in the human microbiome reduces the pH between the end of the small intestine and the colon but gradually increases in the colon [8]. Knowing this pH value, the researchers began to study the pH-dependent colon delivery system. The basic mechanism of the system is to use an enteric coating or pH-dependent polymers. This system is often abused the accepted view is that the pH of the human digestive tract gradually increases from the stomach small intestine at the site of digestion and then increases in the distal ileum [9].

Therefore, pH-dependent manufacturing of colon targeted delivery systems the polymer can withstand lower pH in the stomach and proximal portion of the small intestine protects the active ingredients from these acidic pH values. It decomposes at the neutral or weakly alkaline pH in the terminal ileum, release the active ingredients. The stomach pH range is 1.5 to 2.0 during fasting, food intake will increase the pH of the stomach [10]. Colonic pH range is also gets affected by hydration levels, gastrointestinal disorders, food intake, and microbial metabolism. Also, some biological activities based on polysaccharides-based ingredients can change the pH of the colon. For example, the bacteria in the large intestine produce lactic acid by fermentation of lactulose, which lowers the pH of the large intestine [11]. Therefore, the pH-dependent delivery system protects the active substances in the stomach, and in the proximal small intestine, it can dissolve in the lower part of the small intestine before reaching the colon.

3.3 Colonic Fluid Volume

The average intake of food by humans is about 1.5 kg per day, composed mainly of undigested proteins, carbohydrates, and fat. These food ingredients can act as substrates for microbial enzymes in the colon [12]. The colon has a high water absorption capacity and can absorb approximately 90% of the water that enters the colon [13]. The volume of colon fluid is calculated at 1-44 ml, with an average volume of approximately 13 ml [14]. Due to this low volume of colonic fluids, the dissolution of drugs in pharmaceutical forms becomes challenging and can affect the local bioavailability of the drug.

3.4 Viscosity of Colonic Luminal Contents

Due to its high water absorption capacity, the viscosity of the colon lumen content is higher than that of the upper GIT content, which presents a problem in the dissolution of the delivery system. Also, as the ascending colon progress to the descending colon, the viscosity of the content gradually increases, thus reducing the dissolution and mucous absorption of the drug [15]. Viscosity also affects the penetration of the drug into the disease-causing bacteria in the colon. It was shown that the mobility of the bacteria in the colon depends on the viscosity of the colon contents [16].

3.5 Colonic microflora and enzymes

There are many anaerobic and aerobic bacteria are present along the entire length of human GIT. Intestinal enzymes are used in various parts of the GIT to trigger the drug's release. These enzymes are generally derived from the colon's abundant gut microflora. These enzymes are used to degrade coatings or matrices and break the bonds between the inert carrier and the activator. More than 400 different bacteria have been discovered, of which 20-30% belong to the genus bacteroids. The concentration of bacteria in the human colon is approximately 1000 CFU / mL. The most important anaerobic bacteria are Bacteroides, Bifidobacterium, Eubacteria, Peptococcus, Streptococcus peptide, Photococcus, and clostridium [17].

3.6 Drug absorption in the colon

The drug is passively absorbed via the paracellular or transcellular pathways. Transcellular absorption involves the delivery of drugs through cells, it is the route followed by most lipophilic drugs, and paracellular absorption involves the transport of drugs through narrow junctions between cells and followed by most hydrophilic drugs. If the drug passes slowly through the colon, the contact time between the medication and the mucous membrane is longer than the small intestine. As water is absorbed by the colon, the colon's content becomes more viscous. This decreases the dissolution rate and decreases the diffusion of the dissolved drug through the mucosa.

3.7 Formulation Factors

The formulation factors that affect the distribution and bioavailability of the drug in the colon include the drug's physical-chemical properties, dose, and dosage form factors. Due to the

small amount of colon fluid (1-44 ml) available for dissolution, the solubility and dosage of the drug are important factors for colonic bioavailability. The potent drug budesonide (in a 9 mg dose) is sparingly soluble in water, but is well absorbed by the colon and has been used successfully in the treatment of ulcerative colitis (UC) [18].

In comparison with budesonide (0.24 mg/ml), the solubility of mesalamine (3.64 mg/ml) is much greater. However, its dose is also much higher (4.8 g per day), which is the rate-limiting factor of colonic absorption. Useris® is a delayed-release tablet based on multiple matrices (MMX) that guarantees the release of the medication in the colon. EntocortEC® is a capsule that releases drugs into the ileum to treat Crohn's disease (CD) [19].

4. CRITERIA FOR SELECTION OF DRUG FOR CDDS

The best drug candidates for colon targeted drug delivery system are those that contain peptides and are poorly absorbed by the stomach or intestines. The drugs used to treat irritable bowel syndrome (IBS), ulcerative colitis, diarrhea, and colon cancer are ideal candidates for local colon administration [20]. The criteria for the selection of drugs for CDDS are summarized in Table 2. [21- 23] Drug carriers are another factor that affects CDDS. The choice of the carrier of a particular medication depends on the physical and chemical properties of the medication and the disease in which the system is used. Factors such as medicinal chemistry, stability, partition coefficient, and choice of the type of absorption enhancer will affect the choice of the carrier. Also, the choice of drug carrier depends on the functional group of the drug molecule [24]. For example, the drug's aniline or nitro group can be used to connect it to another phenyl group via an azo bond. Carriers, (which can be used as substrates, hydrogels, or coatings) containing additives (such as polymers) affect the release performance and the effectiveness of the system [20].

Table No. 2: Criteria for the selection of drugs for CDDS

Criteria	Pharmacological class	Non-peptide drugs	Peptide drugs
Drugs used for local effects in colon against GIT diseases	Anti-inflammatory drugs	Oxyprenolol, Metoprolol, Nefidipin,	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 the 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, sermorelin, Saloatonin
Drugs for targeting	Antiarthritic and antiasthmatic drugs	Prednisolone, hydrocortisone, 5-Amino-salicylic acid	Somatropin, Urotoilitin

5. DRUG DELIVERY TECHNOLOGIES FOR COLON-SPECIFIC TARGETING

5.1 pH-dependent delivery systems

The pH of a healthy stomach varies from 1 to 4 but rises to 6 in the proximal small intestine and around 7.4 in the distal small intestine. From the ileum to the colon, the pH drops and increases steadily again throughout the colon [25]. This phenomenon can be exploited to deliver drugs directed to the colon by coating tablets, capsules, or pellets with a pH-sensitive polymer. These polymers are not soluble at low pH, but soluble at neutral or slightly alkaline pH, which protects the drug from the acidic pH of the stomach and provides targeted delivery

to the colon However, intestinal pH is not reliably stable, is frequently affected by diet, disease, and other factors and shows great variability between individuals [26]. This can cause the formulation to dissolve prematurely in the small intestine and therefore can result in replicated colonic distribution. In addition to affecting the dissolution of the pH-dependent coating of the delivery system, the decrease in colon pH observed in the irritable bowel syndrome (IBS) also affects the solubility of the therapeutic agent in the colon fluid, resulting in a decrease in permeability. Methacrylic acid (also known as Eudragit®-Polymer) is the most commonly used pH-sensitive polymer [27]. Eudragit L (soluble at pH 5.5-6), Eudragit S (soluble at pH 7), and Eudragit FS (soluble at pH 7) are generally used alone or in combination to obtain the best dissolution rate [28,29].

In addition to Eudragit, there are other pH-sensitive polymer coatings for application to the colon. Hydroxypropyl methylcellulose acetate succinate (HPMC-AS) and cellulose acetate phthalate (CAP) [30-32].

The Colo Pulse technology is a classic example of a pH-responsive system, but due to the inclusion of other swelling disintegrating agents (croscarmellose sodium) in the coating or matrix, resulting in faster and more pulsatile drug release than other pH-dependent systems [33]. Vcaps® Enteric and entrinsic™ capsules by Capsugel are essentially enteric-coated capsules that provide intestinal protection without the use of functional coatings and delayed-release in the gastrointestinal tract. Both capsule technologies were launched in 2015 and 2016 and are likely to replace standard coated capsules to provide better protection and drug delivery. The capsule is composed of a mixture of pH-sensitive polymers, such as HPMC and HPMC-AS. The results of a study on the intrinsic ™ capsules showed that the capsules increased the bioavailability of the drug in humans, thus ensuring that there is no gastric release and rapid release in the small intestine [34].

5.2 Time controlled or Time-dependent

A time-controlled system helps to synchronize medication administration at pre-selected times so that patients can receive the medication when needed or arrive at a pre-selected location within the GIT. Therefore, these systems are particularly useful in the treatment of diseases that depend on circadian rhythms. Time-controlled colon delivery formulations are also delayed-release formulations and delays in drug delivery are time-based.

In these systems, the location of the drug release is determined by the transit time of the drug within the GIT, which makes it difficult to develop a delivery system to achieve the accurate

release of the drug in the colon. Ideally, the formulation is designed so that the delivery site (i.e. the colon) is not affected by gastric emptying time, gastric and small intestine pH or bacteria in the colon of an individual. On average, the oral dosage form takes about 3 hours to travel the length of the small intestine to the beginning of the colon. Transit time through the small intestine is relatively consistent compared to the rate of gastric emptying, (Gazzaniga et al., 1994; Fukui et al., 2000; Vassallo et al., 1992; Vonderohe et al., 1993).

The system in the form of a tablet formulation is capable of sustained release of drugs into the colon via a time-dependent explosion mechanism. The declaration consists of three parts:

1. A center containing drugs and swelling excipients

2. An internal semipermeable polymer film containing a plasticizer that allows water to enter, but prevents the drug from diffusing.

3. An external enteric coating that dissolves at pH 5.5 and above. The external enteric coat holds the tablet intact until it reaches the small intestine. After reaching the small intestine, the enteric coating dissolves and allows the gastrointestinal fluid to diffuse through the semi-permeable membrane to the core. As a result, when the tablet passes through the small intestine, the core swells. Finally, after 4-6 hours in the small intestine, the swollen core brokes through the semi-permeable membrane and releases the drug into the colon [35-38].

5.3 Microflora-activated release

Colon microflora is a complex ecosystem that contains many different bacteria. The main source of energy for these bacteria is the fermentation of various types of substrates that reach the colon without being digested. For this reason, microflora produces a different polysaccharide degrading enzyme including different polysaccharides [39]. The use of polysaccharides in the coating allows the administration of drugs directed to the colon. Many polysaccharides, such as xanthan gum, guar gum, amylose, dextran, pectin, galactomannan, and chitosan, can be used as drug delivery systems targeting the colon [40]. In addition to polysaccharides, coatings of various azo polymers for colon delivery were also evaluated. These molecules are cleaved by the azoreductase produced by the microflora [41].

An example of a commercial microflora-activated delivery system is the COLAL® coating system, which consists of ethylcellulose and a specific form of amylose (derived from starch) called "glassy amylose". Glassy amylose will not be degraded by human amylase in the

digestive tract but will be digested by bacterial enzymes from the colon. To avoid premature drug release, ethylcellulose must be added to control swelling [42]. Further development of this approach is Phloral® technology, which provides a delivery method that mixes pH and microflora-activated delivery method. The dosage form is coated with a mixture of Eudragit S, amylose, and ethyl cellulose. Another concept of a delivery system is CODES ™ (colon Target Delivery System) [43]. Which combines the triggering of microbial flora and pH-sensitive mechanisms. The center includes the drug and the disaccharide lactulose and is covered with a film of Eudragit E acid-soluble (soluble at pH 5). The outer layer of enteric Eudragit L dissolves in the small intestine, exposing the acid-soluble coating. Colonic bacteria digest lactulose to produce organic acids, thereby lowering the pH around the tablet. This will dissolve Eudragit E and release the medication [44].

TARGIT® is an enteric-coated starch capsule system designed to target specific parts of the colon, combining sequential pH and microflora-dependent release. The coating consists of a mixture of pH-sensitive polymers and has been selected to provide a coating that begins to dissolve in the small intestine. The choice and thickness of the coating polymer determine the release site in the gastrointestinal system. The degradation of starch capsules is attributed to the colonic microflora. Since the drug formulation does not affect the dissolution of the TARGIT coating and, therefore, its in vivo performance remains unchanged, the use of coated capsules as a targeting mechanism is very attractive. There is a large amount of data available to demonstrate the ability of coated capsules to deliver medications to the colon [45].

Recently, a double-coated colon-specific drug delivery system has been developed. It consists of a coating on the tablet core based on a chitosan-based polymer containing citric acid for microclimate acidification, accompanied by an enteric coating. This technology provides controlled drug delivery by inhibiting the release of drugs into the stomach and small intestine and slowly releasing drugs into the colon with the help of chitosanase produced by microorganisms [46]. In the case of active IBD, frequent diarrhea can cause the loss of colonic flora and prevent the site-specific release of this delivery system. To overcome this problem, in recent studies, probiotics are co-administered with tablets that include a core of guar gum and an outer layer of enteric coating.

5.4 Prodrugs

Prodrugs are inactive derivatives of drug molecules that release their active ingredients when hydrolyzed by enzymes such as those in the colon [47]. To optimize the administration of medications specifically to the colon, the extent of this hydrolysis must be minimal in the upper gastrointestinal tract and more extensive in the colon. Azo conjugates are the most studied group of these compounds [48, 49]. However, this is not a very flexible method, as it depends on the functional group of the drug molecule [50]. Kim and others synthesized a metronidazole prodrug. When placed in the contents of the rat cecum, it is metabolized to the active drug metronidazole [51]. Unlike metronidazole, the prodrug is not metabolized in the small intestine and its systemic absorption is much lower than that of oral metronidazole [51]. In another study, Kim et al. prepared a metronidazole prodrug using the sulfate group, indicating that the preparation remained intact in the upper intestine, but was cleaved in the presence of the contents of the rat's cecum to release the active metronidazole. Similar to the original prodrug, the combined prodrug has much less degradation and absorption in the small intestine than the active drug after oral administration. Therefore, very small amounts are absorbed by the system circulation [52].

Vaidya et al. using a prodrug method in which metronidazole is coupled to pectin, the release of the drug in this formulation was compared to the release of the drug in pectin microspheres that physically entrapped the drug [53]. Compared to pectin microspheres containing metronidazole, the prodrug pectin-metronidazole (PT-ME) has been shown to significantly reduced drug release from the upper GIT. In vitro and in vivo studies have shown that under acidic pH, the PT-ME prodrug did not release the drug, but the metronidazole entrapped by the pectin microspheres released almost 100% in the same environment a significantly higher fraction of the drug was released from the PT-ME prodrug in the colon [53].

Another way to help drug preparation maintain its intactness when passing through the stomach and small intestine is to covalently linking to a carrier. The drug can be linked with carrier molecules, such as cyclodextrin, glucuronide, dextran, amino acid. It can also be connected to the carrier via an azo connection. All of these bonds are broken by bacteria and enzymes in the colon [54]. Modasiya et al. Using sodium alginate (Na-Alg) and hydroxyl propyl methylcellulose (HPMC) as carries prepared the matrix, enteric-coated, and compression-coated tablets of curcumin, for delivery to the colon has been studied [55].

The in vitro results showed that, under simulated conditions of the stomach and small intestine, the drug was quickly released from the matrix and enteric-coated tablets. It has also been observed that elevated levels of HPMC significantly limit the release of curcumin in the upper gastrointestinal tract and, in particular, facilitate the release of curcumin to the colon.

5.5 Pressure Controlled Drug-Delivery Systems

Due to peristalsis, the pressure in the colon is greater than the pressure in the small intestine. Takaya et al., Developed a colonic delivery pressure controlled pressure, prepared with ethyl cellulose, which is insoluble in water [56]. In such a system, due to pressure in the lumen of the colon, the release of the drug occurs after the water-insoluble polymer capsule disintegrates. The thickness of the ethylcellulose film is the most important factor in the disintegration of the drug [57,58]. The system also appeared to depend on the size and density of the capsule. Due to the reabsorption of water in the colon, the viscosity of the content in the colon lumen is greater than that of the small intestine. Therefore, it can be concluded that drug dissolution in the colon can present problems related to the colon-specific oral drug delivery systems. In single-unit ethyl cellulose pressure controlled capsules, the drug is in the liquid. When pressure-controlled capsules are administered to humans, a 3-5 hour delay is observed related to the absorption of the drug [59].

5.6 Osmotically controlled system (ORDS- CT)

OROS-CT (Alza Corporation) can be used to target drugs locally to the colon to treat the disease or achieve systemic absorption, otherwise, it cannot be achieved (Theeuwes et al., 1990).) The OROS-CT system can contain a single osmotic unit or 5-6 push-pull units, each unit is 4 mm in diameter and encapsulated in a hard gelatin capsule. Each two-layer push-pull unit has an osmotic push layer and a drug layer surrounded by a semi-permeable membrane. An orifice is drilled through the membrane next to the drug layer. After swallowing OROS-CT, the gelatin capsule containing the push-pull unit dissolved immediately. Due to the drug-resistant enteric coating, each push-pull unit cannot absorb water in the stomach acidic aqueous environment and does not release medications. When the device enters the small intestine, the coating dissolves in a higher pH environment (pH> 7), water enters the device, causing the osmotic push compartment to swell and simultaneously creates a flowable gel in the drug compartment. The expansion of the osmotic push compartment expels the drug gel from the orifice at a certain rate, which is precisely controlled by the rate of water transport through the semipermeable membrane.

To treat ulcerative colitis, the gastric delay of each push-pull device is designed to be 3-4 hours to avoid the release of medication to the small intestine. When the unit reaches the colon, the drug begins to be released. The OROS-CT device can maintain a constant rate of release in the colon for up to 24 hours and can also deliver medications in a short period of 4 hours. Recently, new phase transited systems have emerged, which are expected to be excellent tools for targeting drugs to the colon. Several methods of in vitro and in vivo assessment have been developed to assess the efficiency and stability of the CDDS. Gastrointestinal pressure is another mechanism used to initiate the release of drugs distal part of the intestine [60].

5.7 Novel Colon Targeted Delivery System (CODESTM)

CODESTM is a novel CDDS technology designed to avoid the inherent problems associated with pH or time-related systems. CODESTM is a method of combining pH-dependent and microbially triggered CDDS. It has developed using a unique mechanism involving lactose aldehyde, which triggers the release of drugs in specific parts of the colon. The system consists of a conventional tablet core containing lactulose. Lactulose is first coated with Eudragit E, an acid-soluble substance, and then with Eudragit L, an enteric substance [61,62]. The premise of this technology is that the enteric coating can protect the tablet when passing through the stomach and dissolve it immediately in the upper part of the small intestine. Second, the coating of acid-soluble substances can protect the formulation by passing through the alkaline pH of the distal small intestine [63]. When the tablet reaches the colon, bacterias break down the polysaccharide (lactulose) into organic acids via enzymes. This causes the pH around the system to drop enough to allow the acid-soluble coating to dissolve and subsequently release the drug [64].

6. EVALUATION OF COLON-TARGETED DELIVERY SYSTEM

A successful colon-targeted delivery system can maintain the integrity and activity of the bioactive compound in the physiological environment of the stomach and small intestine, but release the active ingredient into the colon. Several in vitro / in vivo evaluation studies have been proposed to study the release mechanism, the passing behavior of the dosage form, and the physiological effect of the encapsulated biologically active compound to examine the colonic efficiency of the carrier.

6.1 *In-vitro* evaluation methods

Currently, there are no standardized evaluation methods for evaluating drug delivery systems targeting colon in vitro. The ideal in vitro model requires conditions for gastrointestinal stimulation, such as pH, volume, agitation, pressure, bacteria, enzymes, and other food ingredients. Also, these conditions are highly sensitive to several factors (such as diet, physical stress, illness, etc.) which makes it more difficult to design standard in vitro assessment models. In recent years, although not ideal, some in vitro models have been applied, as shown in Figure 2.

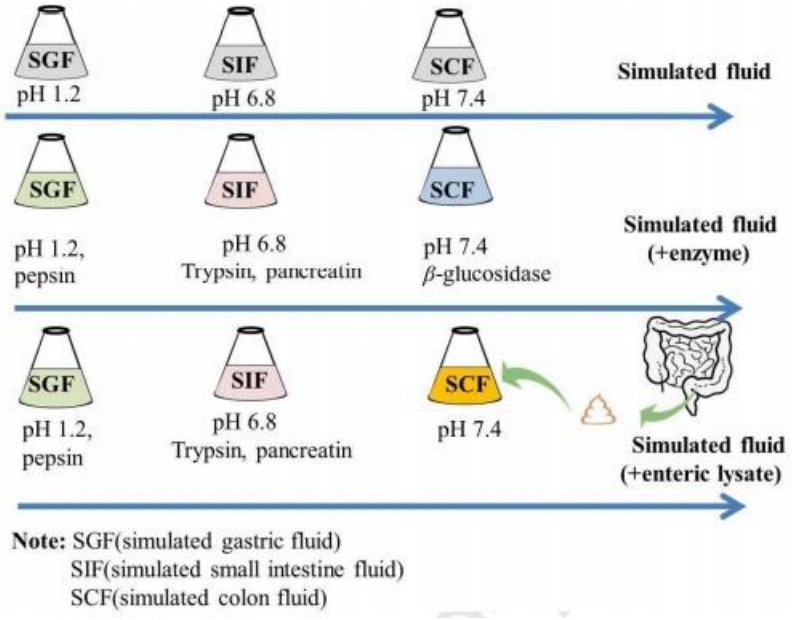

Figure No. 2: *In-vitro* dissolution test models [7]

6.1.1 *In-vitro* dissolution tests

The dissolution test is probably the simplest and most widely used method for evaluating oral delivery systems, including delivery systems that target the colon. The method is considered reproducible, scientifically valid, and biologically relevant. In general, USP recommends the use of four dissolution apparatus: basket, shovel, reciprocal, and flow cell to evaluate different dosage forms [65]. The dissolution test of colon-targeted vehicles in a variety of media has been reported, which simulates physiological conditions (such as pH and time of propagation) at various locations in the gastrointestinal tract.

For instance, pH 1.0 for 2 hours and pH 6.8 for 3 hours can simulate the gastric conditions and the jejunal region of the small intestine respectively, and pH 7.4 can simulate the large intestine (Barba, Dalmoro, D'Amore and Lamberti, 2013) [66]. Also, a kinetic studies study was conducted to study the mechanism of release of bioactive agents in various carriers targeted to the colon. Table 3 shows the corresponding equations and principles of five mathematical models, including zero-order model, first-order model, Higuchi model, Rigger Peppers model, and Weibull model (Sinha, Ubaidulla and Nayak, 2015; Dodov et al., 2009) [67]. Then, the regression analysis is performed on the release data of different simulated fluids, and the model with the highest correlation coefficient (r) is considered the best model.

Table No. 3: Different release models commonly applied for characterizing the release profile of the bioactive compounds

Mechanisms	Equations	Application	Release Mechanisms
First-order	$Q=1-\exp(kt)$	One release mechanism	Dissolution
Higuchi	$Q = kt^{1/2}$	One release mechanism	Fick diffusion mechanism
Weibull	$Q=1-\exp(-at^{b})^{B}$	More than one release mechanism	b<0.75, Fick diffusion mechanism 0.75 ≤b ≤1, Case II transport; b>1, Complex release mechanism
Ritger-Peppas	$Q = kt^{n}$	More than one release mechanism	n<0.45, Fick diffusion release; 0.45 ≤n ≤0.89, anomalous (non-Fickian) transport; n=0.89, zero-order (case II) release; n>0.89, super case II transport
Peppas-Sahlin	$Q=k_1t^{1/2}+k_2t^{C}$	Quantify the contributions of erosion mechanism and diffusion mechanism	K1/k2<1, erosion predominates; K1/k2=1, diffusion equates erosion; K1/k2>1, diffusion predominates

Notes: A Q=Mt/M∞ Mt and M∞ represent the cumulative amount of the bioactive compounds released at time t and the total amount of bioactive compounds loaded in the vehicles, respectively; k, the release rate constant;

B a, scale parameter; b, shape parameter.

C k1 and k2 are the diffusion and erosion terms, respectively.

6.1.2 Modified *in-vitro* dissolution tests (containing enzyme)

In some *in-vitro* studies, the simulated solution consisted only of buffers with different pH values (Petrovic et al., 2013) [68]. However, they may not accurately reflect the true release properties of the human gastrointestinal tract. In vitro release experiments on buffers containing pepsin, trypsin, pancreatin, β-glycosidase, and other buffers were performed by several researchers and the release of components was assessed (Bokkhim, Bansal, Grondahl, and Bhandari) [69]. In general, it is believed that the amount released over some time is proportional to the rate of degradation of the carrier polymer. The amount of biologically active compound released into the enzyme-rich medium is generally greater than the amount released in the enzyme-free buffer. The addition of β-glucosidase helps to mimic enzymes produced by microorganisms present in the colon. Therefore, the enzyme-rich medium is primarily used for evaluating systems based on the microflora activation mechanism.

6.1.3 Modified *in-vitro* dissolution tests (containing enteric lysate)

The gastrointestinal tract is so complicated that the simulated medium cannot accurately represent the real state even in presence of enzymes. Therefore, in addition to in vitro dissolution tests with enzymes as mentioned above, the researchers also used the cecal content of animals (Rajyalakshmi & Muzib, 2015) [70] or human feces (Vieira et al., 2013) [71] slurries in dissolution medium. One example of this is Ilango et al. (2010) evaluated Tablets containing microbially activated material in dissolution medium containing rat cecal content [72]. These researchers found that the maximum release with rat cecal matter in 10 hours was 98%, but after 10 hours, the amount of release without rat cecal matter was only 47%. Therefore, the composition of the stimulating release medium has a significant effect on the release of the loaded biologically active compound, especially in the distribution system caused by microorganisms. The results were similar to another study conducted by Zhang et al. (2011) [73]. These results also indicate that it is very important for researchers to select

the correct media to accurately assess the release profile of physiologically active compounds in the colon-directed transporter.

6.2 *In-vivo* evaluation methods

In-vivo studies are generally performed to evaluate site-specificity and the related physiological effectiveness of the delivered biologically active compound and to prove the processing capacity of the resulting dosage form. Due to their anatomical and physiological conditions and the microflora similar to the human gastrointestinal tract, a variety of animals such as rats, dogs, pigs, guinea pigs, and rabbits have been used to evaluate delivery behavior. Several imaging techniques were used to clarify the delivery behavior of the vehicle and the release behavior of the active compound physiologically. Also, an *in-vitro* study was carried out to examine the distribution of physiologically active ingredients in various gastrointestinal tissue.

6.2.1 *In-vivo* imaging

The aim of the colon targeted system is to absorb and/or deliver physiologically active compounds to functional sites. Only in vitro tests have been proposed and performed to evaluate vehicles based on various mechanisms, but it is impossible to accurately understand the delivery and disintegration behavior of these systems. In such a case, some imaging techniques were applied to observe the movement of a transport vehicle.

6.2.2 X-rays

X-ray imaging is the most commonly used technique to visually identify different vehicle stages, not only for humans but also for the entire gastrointestinal tract of animals. Yassin et al. (2010) designed a colon-based delivery system targeted to the colon and extensively studied its resistance to the environment of the stomach and small intestine and the selective disintegration of the system in the colon [74]. They observed complete disintegration of the tablets 10 hours after administration, and similar results have been reported in the Omar group (Omar, Aldosari, Rekai, and Gohary, 2007) [75].

In another report, X-rays were used to monitor the specificity of the position, position, and vehicle integrity in the rabbits. (Ilango et al., 2010) [76]. Nandy, Verma, Dey, and Mazumder (2014) also demonstrated the feasibility of monitoring X-rays for changes in microspheres directed at the colon [77]. The results of the X-ray images showed that the swelling layer was

eroded from the external surface and decreased in size after reaching the colon site (6 hours). Therefore, X-rays are considered a good technique to identify the location, swelling, and integrity of the intermittent colon release vehicle in GT.

6.2.3 Gamma scintigraphy

Gamma scintigraphy is another technique used to observe the in vivo fate of vehicles in terms of gastrointestinal resistance and matrix integrity *in-vivo*. Asghar & Chandran (2011) reported that the vehicle remained intact when passing through the gastrointestinal tract and colon [78]. The imaging results showed that the average gastrin emission was 1.87 ± 0.55 hours, and the flow of the small intestine was 3.1 ± 1.3 hours, with colon retention. . 16.67 ± 1.6 hours each. The arrival time of the colon is roughly 5.0 ± 1.52 hours, suggesting that the in vitro release profile and the in vivo transit time are well associated. On the other hand, other researchers performed gamma scintillation to verify the practicality of the delivery system directed to the projected colon.

6.2.4 Fluorescent imaging

Fluorescent imaging is another imaging technique used for the evaluation of the delivery system. In this, the delivery vehicle was observed by fluorescence imaging with a fluorescence image analyzer. The intensity of fluorescence in the colon weakened as a function of transit time, indicating that the microcapsules might be excreted from the body. studies were carried out by Bie, Chen, Li sum Li (2016) and (Wang, Wang, Zhou, Gao, & Cui, 2016). On microspheres labeled with Fluorescent imaging to monitor the delivery behaviors *in-vivo*. The results demonstrated that the retention time in the colon was more than 12 h [79,80].

7. CONCLUSION:

The colonic region of the GIT is increasingly becoming an important place for drug delivery and absorption. CDDS can provide patients with significant therapeutic benefits locally and systemically. In a system that uses natural substances degraded by bacterial enzymes in the colon, it is more likely to achieve colon specificity. Given the complexity of colon-specific drug delivery systems and the uncertainty of current dissolution methods in establishing possible *in-vivo* / *in-vitro* correlations. Developing a dissolution method that combines the physiological characteristics of the colon is a challenge for pharmaceutical scientists and to verify residues and can be used routinely in the industry to assess CDDS.

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