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COLON DRUG DELIVERY SYSTEM, ADVANCE DEVELOPMENT AND EVALUATION: A REVIEW

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ABSTRACT: Colon targeted drug delivery system is a significant part of the pharmaceutical dosage form. Because the colon targeted formulation system only responds to the colon-specific physiological conditions, a triggering mechanism is required. Site of colon provides local and systemic drug delivery. Inflammatory bowel disease can be treated by localized delivery of drugs. The systemic side effect can be decreased by aiming the medications directly to the colonic cycle. Rectal and oral formulations are the major drug targeting strategies that target the colon by pressure, pH, and micro-flora triggered the release of the drug. Formulation of colon targeted system is a complicated process involving substantial efforts. This article discusses the advantages, limitations, primary and advanced approaches, and evaluation of colon-specific systems and provides information regarding some of the formulations available in the market to treat colon-related disorders. This article also focuses on current and future prospects in the area of colon-targeted formulations.

INTRODUCTION: Colon targeted formulation system is the delivery of active agents in the large intestine (colon) i.e., into the lower gastrointestinal tract1. Colon-specific formulations are favorable in the therapy of ailments such as ‘inflammatory bowel disease’, ‘irritable bowel syndrome’, ‘ulcerative colitis’, *etc*. Colon targeted formulation system is helpful in lowering the systemic side effects [2]. Colon-targeted delivery of the drug is also helpful in transporting proteins and peptides.

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In the treatment of inflammatory bowel disease, colon-targeted drug formulations are fabricated to transport anti-inflammatory medications to the site of disease, and thus, systemic absorption of medication should be lowered as they may cause undesirable systemic side effects [3, 4].

The designing of a colon-specific formulation is a bit complex and includes various approaches, one of which is multiparticulate approach. A multi-particulate approach consists of pharmaceutical formulations such as pellets, granules, spheroids, nanoparticles, microparticles [5]. As the colon is distally located in the gastrointestinal tract, the colon targeted formulation system should not allow the medication to release in the stomach and small intestine [6]. There are various challenges in the development of colon-specific system.

One of the utmost challenges which is faced in the formulation of colon targeted formulation system is the impact of the disease on the delivery system *e.g.,* patients with inflammatory bowel disease (IBD) has the lower luminal pH of the distal intestine as compared to healthy volunteers.

Drug Absorption through Colon:
Colonic Absorption Involves Two Processes:

- Transcellular transport (drug moiety travels through colonocytes)
- Paracellular transport (drug moiety travels between adjacent colonocytes)

Many lipophilic drugs are absorbed through transcellular absorption as it involves the passage of drugs through the cells. Most of the hydrophilic drugs are absorbed through paracellular transport, as it means the transport of drugs through the intercellular space between the cells. Drugs that show good absorption include diclofenac, theophylline, ibuprofen, metaprolol. Drugs that show poor absorption include atenolol, furosemide, buflomedilpiretanide [7].

Microflora of Colon: The design of a polysaccharide-based system is based on the availability of colonic anaerobic bacteria. More than 400 named bacterial species with a concentration of 1011 to 1012 CFU/ mL with Bacteroids, Bifidobacterium, Eubacterium, Lactobacillus is present in the human colonic region. Many processes takes place in colon, such as the fermentation of carbohydrates and proteins, bile acid and steroid transformation, activation, and degradation of mutagenic metabolites, etc. by the enzymes that these bacteria generate. Enzymes responsible for the disintegration of polysaccharides involve β-D-fucosidase, β-D-galactosidase, β-D-glucosidase, β-D-xylosidase, α-L-arabinofuranosidase. Various factors such as diet, age, diseases, geographic regions affects the composition of colonic anaerobic bacteria [8].

Advantages of Colon Drug Delivery System [7]:

- Bioavailability is increased.
- Dosing frequency is reduced.
- Dose size is reduced.
- Patient compliance is improved.
- Formulation development is flexible.
- It provides site-specific delivery of drug in its intact form.
- Adverse side effects are lowered.
- It protects the mucosa from drugs that cause irritation.
- It is economical for patients.

Limitations of Colon Drug Delivery System [7]:

- Dose loading is low.
- There is a high requirement for excipients.
- It has multiple formulation steps.
- There is a large number of the process variable.
- It requires advanced technology.
- There is a lack of reproducibility and efficacy.
- Manufacturing of colon drug delivery system requires a skilled person.

Factors Affecting Colon Drug Delivery System:
Colon Anatomy and Physiology: The stomach, small intestine, and large intestine define the gastrointestinal tract. The large intestine is classified into colon, rectum anal canal. The colon is around 5 feet in length. The drug should not absorb from other parts of gastrointestinal tract except the colon. In small intestine, there should be negligible degradation of drug. The release of medication from the formulation system into the large intestine should be at a controlled pace [9].

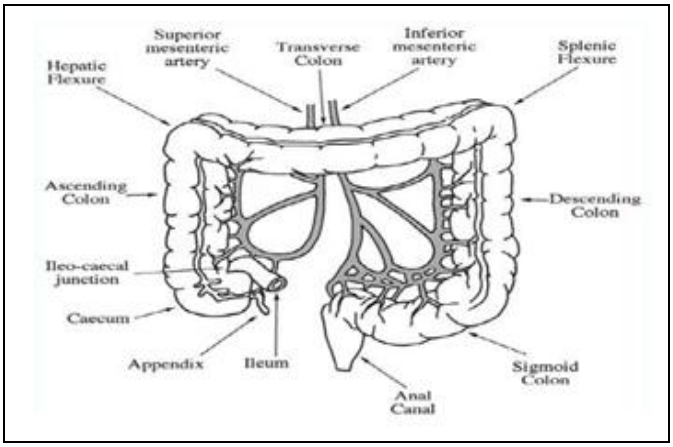

FIG. 1: VARIOUS PARTS OF COLON

TABLE 1: LENGTH VARIOUS SEGMENTS OF COLON 10

S. no.	Large Intestine	Length (cm)
1.	Cecum + ascending colom	28.9
2.	Descending colon	21.8
3.	Transverse colon	50.2
4.	Sigmoid colon	35-40
5.	Rectum	12
6.	Anal canal	3

pH Levels in the Gastrointestinal Tract: In the formulation of colon-focused drug delivery formulation, pH levels of all parts of gastrointestinal tract is crucial [11]. Carbohydrate-rich diet affects the pH of the colon due to the fermentation of polysaccharides by micro-flora of colon. Colonic pH also gets affected by polysaccharide-based drugs, *e.g.,* laxative drugs like lactulose [12, 13]. The pharmacokinetic and pharmacodynamic action of a colon-specific system is also affected by the pH of colon.

TABLE 2: pH OF DIFFERENT SEGMENTS IN GIT [14]

Sr. no	Part	pH
1.	Stomach	1-2
2.	Proximal small intestine	6.5
3.	Distal small intestine	7.5
4.	Ascending colon	5.7
5.	Transverse colon	6.6
6.	Descending colon	7.0

Transit Time: Movement of the drug and contents through the large intestine is steady comparing with other segments of GIT. The transit schedule of colon ranges from 20 to 30 h. In the presence of disease, the colonic transit time is increased *i.e.,* 50 to 70 h. Longer transit time with longer residence time leads to higher absorption of the drug from the colon drug delivery system [15].

TABLE 3: TRANSIT TIME OF DIFFERENT REGIONS IN GASTROINTESTINAL TRACT [14]

S. no	Part	Transit time (h)
1.	Stomach	1-2
2.	Small intestine	3-4
3.	Right (Ascending + portion of transverse)	11.3
4.	Left (Descending + portion of transverse)	11.4
5.	Rectosigmoid colon	12.4

Colonic Fluid Volume: As colonic fluid volume is approximately found to be 1-45 ml [16], the bioavailability of the drug may get affected because of the low colonic fluid volume [17].

Colonic Enzymes: The colon comprises of varying species of aerobic and anaerobic microorganisms comprising various hydrolytic and reductive metabolizing enzymes [18, 19].

The metabolism of xenobiotic and biomolecules are catalyzed by colonic enzymes [20]. Drug metabolism by colonic enzymes leads to the development of pharmacologically active, inactive metabolites, but sometimes it also results in the formation of harmful metabolites [21, 22].

Viscosity of Colonic Contents: As the contents travel from ascending to descending colon, the viscosity of the contents increases, which leads to a decrease in mucosal absorption and dissolution of drug [23]. The colonic contents' viscosity is more than upper GIT contents because of the high capacity of water absorption, which poses a challenge for the development of colon targeted formulation system.

Need for Colon Targeted Formulation System:

- Site-targeted delivery of medication to the site of the colon has potential application in treating the colon-related disorder.
- Colon-specific formulation is considered to be beneficial in lowering dosing frequency and systemic side effects [24].
- Protein and peptide drugs can be orally delivered by the help of site-specific colon formulation.
- Prolongation of delivery of drug could also be possible by colon targeted formulation.
- Inflammatory conditions such as 'ulcerative colitis' or 'Crohn's disease can be managed by the achievement of both local and systemic delivery. Usually, glucocorticoids and sulphasalazine are used to treat such inflammatory ailments [25].
- Major diseases of the colon, such as colorectal cancer, can be managed beneficially by the help of targeted delivery of a drug to the site of disease [26].
- Drugs that are prone to chemical or enzymatic disintegration in the upper GIT can be delivered through colon targeted formulation.

Approaches for Design and Development of Colon-specific Drug Delivery System:

A. Chemical Approach:

Azo Conjugates: Sulphasalazine is majorly used in the treatment of inflammatory bowel disease. An oral dose of 85% of sulphasalazine is unabsorbed when it reaches colon, where it gets reduced to sulphapyridine and 5-ASA (5-Amino salicylic acid)

by anaerobic environment. After the evaluation of flurbiprofen by the use of azo-aromatic and pH-sensitive polymer, it was suggested that in the formulation of colon targeted systems, azo-aromatic polymer, and pH-sensitive polymer Eudragit S can be efficiently applied [27].

Cyclodextrin Conjugates: Cyclodextrins are 'cyclic oligosaccharides' that involve 6-8 glucose units through 1, 4glucosidic bonds, and it is used to enhance certain characteristics of medications such as bioavailability, solubility, and stability. These particles are relatively hydrophilic from the exterior and lipophilic from the interior [28]. Nevertheless, they are fermented by colonic bacteroids in tiny saccharides and then get absorbed in the colonic area [29, 30]. The oral consumption of CyD-5-ASA leads to decreased plasma and urine concentration of 5-ASA as compared to 5-ASA only [31].

Glycosidic Conjugates: New colon targeted formulation system is based on the 'steroid glycosides' and the distinct 'glycosidase' action of the colonic bacteroids. As the glycosidic drugs are hydrophilic in nature, they are poorly absorbed from the small bowel [28]. The chief glycosidase identified are D-glycosidase, D-galactosidase, D-xylopyranosidase, L-arabinofuranosidase. These glycosides does not move across the biological membrane upon ingestion because of their bulky and hydrophilic nature [32].

Glucuronide Conjugates: 'Glucuronide conjugation' is the main metabolic pathway of drug. Lower gastrointestinal tract contains a bacteria that produce "β-glucuronidase" and can deglucuronidate various active agents in the intestine. Thus, the active drug is released and reabsorbed by the process of deglucuronidation [33]. This concept is applied for the transporting drug to colon, where the drug is coupled with glucuronide conjugation after oral delivery [34].

Polymeric Pro-drugs: New approaches in colon targeted formulation involve polymers as a carrier for the delivery of the drug to the colon. All-natural and synthetic polymers can be utilized as drug carriers [35]. Polymeric pro-drugs can be formed with azo linkage between the polymer and the drug by using sub-synthetic polymers [36]. Evaluations of different azo polymers as coating material have been performed. Azoreductase is the enzyme that is responsible for cleaving azo polymers in the large intestine. It has been found that peptide capsules coated with azo polymers prevent the digestion of drugs in the stomach and small intestine. When the capsule reaches colon, azo bonds are reduced, and the medication is released [37].

Amino Acid Conjugation: The presence of polar groups, *e.g.*, NH2 and –COOH in proteins, reduces the membrane permeability of amino acids and proteins because of the hydrophilic nature of polar groups. As the hydrophilicity and chain length of carrier amino acid increases, the permeability of amino acids and proteins decreases [38]. Thus, amino acid conjugation results in high enzymatic specificity for hydrolysis by the enzyme of the colon.

Dextran Conjugates: Dextran is a bacteria-based polysaccharide where the monosaccharides are connected by glycosidic linkages. Dextranase is the enzyme that is in charge of the hydrolysis of these linkages. The pro-drug technique of dextran can be applied for colon targeted drug delivery having a carboxylic acid function [41]. In the upper GIT, dextranase has negligible activity, but anaerobic gram-negative bacteria which is found in a high concentration in the large intestine, shows high dextranase activity [39].

B. Pharmaceutical Approach:

pH-Sensitive Polymer Coating: The covering of pH-delicate polymers to the pellets, tablets, and capsules give postponed discharge and shield the dynamic medication from the fluid of gastrointestinal tract. The polymers utilized for aiming medications or in any case ought to have the option to resist the lower pH estimations of the stomach and of the proximal piece of the small digestive system and furthermore have the option to deteriorate at the unbiased of marginally soluble pH of the terminal ileum and ideally at the ileocecal intersection. These procedures dis-seminate the medication all through the digestive organ and enhance the capability of the colon focused on conveyance frameworks. By this approach, the formulation is protected in the stomach and small intestine, but it begins to solubilize when it reaches lower small intestine. So, the formulation will have poor site-specificity [40].

Biodegradable Polymer Coating: The bio-environment of the human gastrointestinal tract is portrayed by the nearness of complex bacteria, particularly the colon that is wealthy in microorganisms that are engaged with the procedure of decrease of a dietary segment of different contents. Medications covered with the polysaccharides, which indicate degradability because of the impact of the microflora of colon, can be utilized to develop formulations for targeting colonic ailments. These microbially-disruptive polysaccharides, particularly 'azo-polymers' have been investigated so as to deliver the orally regulated medication to the site of colon. All things, endless supply of the dose structure through the GIT, it stays unblemished in the stomach and small digestive tract where next to no biodegradable movement is available that hushes up deficient for breaking the polymer layer. Liberation of the medication from azo polymer covered dosage form should happen after reduction and in this manner azo-reductase enzymes available in the micro-flora of the large intestine degenerate azo-bonds [41].

Polysaccharide System: A broad range of hydrolytic and reductive enzymes *e.g.* β-xylosidase, β-glucuronidase, β-galactosidase, nitroreductase, azoreductase, deaminase are produced from microorganisms present in the human body such as Bacteroids, Lactobacillus, Bifidobacterium, Eubacterium, Clostridium. Di-, tri-, and poly-saccharides get degraded by these enzymes. Pectin and xylan are natural polysaccharides that get degenerated in the colon by colonic bacteria. Various polysaccharides present in the diet get degraded by the bacterial enzymes [42]. Thus, these polysaccharides can be applied as potential carriers for colonic distribution of active agents [43]. The widely used polysaccharides for colon-specific drug delivery are alginates, amylose, galacto-mannan, arabinoxyan, inulin, chitosan, pectin, and pectates.

Delayed-Release System: Delayed-release system for colon targeted drug delivery is also known as a time-controlled system in which there is a time-based delay in drug delivery. In this approach, the system is designed in such a way that the individual differences in the gastric emptying rate, availability of anaerobic microorganisms in the large intestine, or pH of the stomach and small intestine do not affect the colonic site. The transit time through the small intestine does not depend on formulation. The designing of a delayed-release system is such that the drug is released after a predetermined lag time. Delayed release formulations usually consist of 4 or 6 h of nominal lag time based on the assumption that this time is needed for the formulation to reach the colonic site [44].

Osmotically Controlled System: Osmotically controlled system comprises osmotic components. The osmotic components are usually applied as either single component or 5-6 push-pull components which are encapsulated in the capsule made of hard gelatin. Such units are bilayered with semi-permeable membrane within. The middle segment of push pull components comprises of film of active agent. There is an aperture in the semi-permeable membrane which is present besides the film of the active agent [45]. During the course of time, the contents expel out through this aperture. After the administration, the capsule containing the push pull components gets dissolved quickly [46]. Once the formulation reaches the small intestine, the coating gets solubilised due to slightly basic pH. Push layer is swelled as the water enters the unit through the aperture in the semi-permeable membrane. As the push layer swell, it makes the drug content to expel out through the aperture. Thus, the osmotic controlled system delivers the drug for up to 24 h at a perpetual rate [47].

Pressure Controlled System: Owing to peristalsis, higher pressures are developed in the large intestine as compared to the small intestine. Pressure controlled colonic delivery capsule has been developed using Ethyl cellulose which do not solubilize in water. Because of the high pressure in the lumen of the colon, the water insoluble ethyl cellulose capsule disintegrates and the drug is released. The major factor for the degradation of the polymer is the thickness of the 'ethyl cellulose polymer membrane' [48]. Another important factor is capsule size and density. O wing to the reabsorption of water from the colon, the viscosity of the luminal material is greater in the large intestine compared with the small intestines. After administration of pressure controlled capsules, lag time of 3 to 5 h in relation to absorption of drug is found [49].

Bioadhesive System: For achieving optimum therapeutic results, some orally administered medication needs high local concentration in the large intestine. Biodhesion is the mechanism by which the formulation stays in contact with certain part of the body for a particular time interval.

The higher residence time of the medication in a particular organ results in increased absorption of poorly absorbable drugs. For bioadhesive systems, a wide range of polymers have been investigated such as polyurethanes, polyethylene oxide-poly-propylene oxide copolymers, poly-carbophils. This system can be applicable for developing colon colon targeted formulation system [50].

Multiparticulate System: This drug delivery system involves pellets, microparticles, granules, nanoparticles, *etc*. This system is preferred over single dosage form as this system reaches the colon rapidly and prolongation of drug release can be achieved. As these systems are smaller in size, so they travel through the gastrointestinal tract smoothly. Multi-particulate systems results in uniform drug absorption at the site of action as they disperse more uniformly in gastrointestinal tract [51].

Colon Specific Polymers: Development of solid oral dosage forms involves the application of natural polysaccharides for colon specific drug delivery [52]. Biodegradable polysaccharides are usually hydrophilic and have restricted swelling capacity in acidic medium.

Different enzymes secreted by bacteria include β-D galactosidase, pectinase, amylase, α-D-xylosidase, dextranase, β-D glucosidase [53]. These poly-saccharides are found in a broad range of structures and are inexpensive. Linear polysaccharides are beneficial to be used in colon targeted formulations as they remain intact in stomach and small intestine but gets degraded when come in contact with colonic anaerobic bacteria [54].

Guar Gum: Guar gum is obtained from the seeds of *Cyomopsis tetragonolobus* (Family: Leguminosae). Guar gum comprises of sugars that are galactose and mannose. Guar gum has potential application in colon targeted system because it gets degraded microbially in large intestine. In a study, guar gum have been utilized as a coating material for the colon targeted delivery of 5-florouracil [55]. Pellets were developed by a coating of guar gum along with pH-sensitive polymers Eudragrit as a copolymer around drug-loaded cores. This study concluded that guar gum film coating worked as a time-controlled polymer until it degraded in the colon by coming in contact with the microbial enzymes present there.

Pectin: Pectin is a linear, heterogeneous polysaccharide comprised of 'galacturonic acid' and its methyl ester. A study has developed colon targeted formulation in which they have used pectin as a polymeric carrier and diltiazem hydrochloride and indomethacin as model active agents [56]. From the *in-vitro* study, it has been concluded that prepared formulations have restricted the release of drugs in the stomach and small intestine, and a higher quantity of drugs is released in the large intestine. Thus, both water-soluble and insoluble drugs can be targeted to the colon by the use of pectin. In another study, it has been found that pectin microspheres have been developed for oral colon delivery of indomethacin by the spray-drying method. Then, these microspheres were cross-linked with calcium chloride. Due to this cross-linking, the release of indomethacin is found to be decreased. The release of the drug from the microsphere was accelerated by the addition of pectinase [57].

Chondroitin Sulfate: Chondroitin sulfate is a soluble mucopolysaccharide that is used as a substrate by *B. thetaiotaoimicron* and *B. ovatusin* the colon [58]. *B. thetaiotaoimicron* and *B. ovatus* present in large colon degrades chondroitin sulfate as it comes in contact with these anaerobic bacteria [41]. Natural chondroitin sulfate is soluble in water, but it is incapable of controlling the release of most of the drugs from the matrix [59, 60]. The highly water-soluble characteristic of chondroitin sulfate hinders in the designing of colon targeted drug delivery system. In a study, a matrix tablet of indomethacin was prepared using chondroitin sulfate along with chitosan as a carrier and binder for site-targeted delivery of the drug to the colon [61]. When chondroitin sulfate was used along with chitosan, polyelectrolyte complexes (PEC) were formed, which confirms its potential for colon-specific drug carrier. This study concluded that cross-linked chitosan and chondroitin sulfate polysaccharides is used to attain colon targeted

delivery of drug [62]. Another study specifies cross-linked chondroitin sulfate for delivery of the drug to the large intestine. Hydrosolubility of chondroit in sulfate was reduced when it is cross-linked with trisodium trim-etaphosphate.

Dextran: Dextran is a highly water-soluble polymer that is available as different molecular weights commercially. It has potential application in the delivery of proteins and peptides [63]. Dextran can be easily conjugated into drugs and proteins as it has a large number of hydroxyl groups. Dextran is a polysaccharide comprising of α-1, 6 D-glucose, and the side chain of α-1,3 D-glucose units [53].

It has been found out that dextran gets degraded by human feces because of bacterial activity [64]. As dextran gets degraded when it comes in contact with microbial enzyme dextranase, which is present in large intestine, this makes it applicable to be used as a polymer carrier for colon targeted formulation [52]. It has been found that conjugation with dextran leads to the alteration of toxicity profile, prolongation of the effect, and reduction in the immunogenicity of the drug. Dextran is used in various studies because of its special characteristics mainly biodegradability, solubility [65].

Cyclodextrin: Cyclodextrin is a cyclic oligosaccharide comprising of 6-8 glucopyranose units attached by D-(14) glucosidic linkage. The central lipophilic cavity of cyclodextrin has the ability to complex with hydrocarbon materials [66]. Due to the availability of colonic anaerobic bacteria in the large intestine, cyclodextrin gets fermented to small monosaccharides and absorbed in the colonic area [67].

In a study, an anti-inflammatory drug was conjugated through an ester or amide linkage with primary hydroxyl groups of alpha, beta, and gamma cyclodextrins. The *in-vivo* studies of these drug-cyclodextrin conjugates were examined in rats for drug release behavior. This study shows that such conjugates have stability in the stomach and small intestine due to which they can be used in the design and development of colon targeted formulation system [68].

Chitosan: Chitosan is a functional linear, polysaccharide comprising of repeated units of (2-amino-2-deoxy-D-gluco-pyranose) which are joined by (1-4) β-bonds. Chitosan is used as an excipient and drug carrier because of its non-toxic, biodegradable, biocompatible, and bioactive properties. The tendency of chitosan to solubilize in acidic media but gets swollen in alkaline pH makes it possible to be applied for colon targeted formulations. Colonic of anti-ulcerative colitis medication is made possible by using chitosan capsule. In this study, 5-Aminosalicylic acid was used as model API. In the presence of rat cecal content, it was observed that the pace of drug release from the chitosan capsule was increased. Thus, the study suggested that chitosan capsules could be a potent carrier for colon-specific drug delivery of anti-inflammatory drugs [69]. A novel dispersion system of chitosan has been developed for colon-specific systems consisting of a drug reservoir and an exterior release rate-regulating layer. This system was prepared by making chitosan dispersion in hydrophobic polymer. It was noted that the thickness of the exterior layer of the dispersion system controls the release of the drug. As the dispersed chitosan dissolves under acidic media, the enteric coating prevents the drug release from the dispersion system in the stomach [70]. Various salts of chitosan were setup by dissolving chitosan in different acidic media [71]. It was concluded from the study that when the drug was mixed with chitosan salts, the release rate of the drug was decreased in acidic and basic pH.

Inulin: Inulin comprises of β-2-1 linked D-fructose molecule and is generally known as naturally occurring glucofructan. In the upper gastro-intestinal tract, inulin has the ability to resist hydrolysis and digestion; when it comes in contact with the colonic anaerobic bacteria, it gets fermented. In a study, hydrogels were developed using inulin for colonic delivery of drugs. From this study, the swelling property of these hydrogels was observed [72]. Various parameter influences the swelling characteristics of hydrogels such as feed concentration of methacrylated inulin, the effect of pH, ionic strength, and degree of substitution. Many researchers have been done for inulinase preparation using inulin hydrogels. From these researches, It has been concluded that hydrogels gets degraded due to the diffusion of inulinase enzyme into hydrogel [73].

Amylose: Amylose is an unbranched linear polymer of glucopyranose units (α-1,4-D-glucose) joined by α-D-(1-4) linkage. It is a component of starch and is obtained from plant extracts. Bacteroids, bifidobacterium cause the degradation of amylose but it is not degraded by pancreatic amylase in its glassy amorphous form. Amylose coating can be done by gelation for the purpose of tablet coating. The coating blend of amylose consists of water-insoluble polymer to control the swelling of amylose. For the purpose of colon targeting, ethylcellulose is added to amylose. *In-vitro* dissolution studies of pellets coated with different ratio of amylose: ethylcellulose blend was performed under simulated gastric and intestinal condition. The result of this study reveals that amylose: ethylcellulose (1:4) blend withstand these conditions over 12 h duration [74].

Nutriose: Nutriose is obtained from dextrin fraction which is obtained from wheat, maize or other edible starches [75]. It is a branched dextrin that has a high content of fiber. It is soluble in water. In a study, a drug-loaded pellet of 5-Aminosalicylic acid was developed by the technique of extrusion-spheronization. Then, these pellets loaded with medication were coated with varying polymeric blends of nutriose: ethyl cellulose. *In-vitro* drug release studies of all the prepared batches were performed under different conditions with the exposure of fresh fecal samples obtained from patients of inflammatory bowel disease under anaerobic conditions. The enzyme formed by the colonic anaerobic bacteria present in the patient's colon with inflammatory bowel disease degrades nutriose. The release of medication from the coated pellets was reduced in the upper GIT, but when the pellets came in contact with the fecal samples, the rate of release of the drug increases. This study concluded that these novel polymeric barriers adapt themselves according to the conditions at the site of action with respect to the microflora in the disease state and pH of the bio-environment [76].

Locust Bean Gum: Locust bean gum comprises natural polysaccharides having a molecular weight of 310000. Locust bean gum is obtained from the seed of the 'Carob' (*Ceratonia siliqua* Linne, Family: Leguminosae), so it is also known as 'Carob gum'. It is asymmetric molecule with branched β-1,4-D-galactomannan units. A study shows that coating blend having locust bean gum and chitosan has the ability to shield the tablet core having active agent during the conditions simulating mouth to colon transit. The drug releases from the degradation of coating by colonic bacterial enzyme. This study suggested that 4:1 ratio of locust bean gum and chitosan coating blend has higher bioavailability and better dissolution profile. Thus, it is a potential polymer to be used for colon targeted formulation systems [77, 78].

Advance Development in Colon Drug Targeting Technologies: There are various approaches or delivery systems available that effectively deliver the drug to the colonic site. Amongst all these approaches, micro-flora activated delivery system was found to be one of the most effective technique in targeting the drug to the site of action as the colonic anaerobic bacteria secretes the enzymes which triggers the release of drug from the formulation system. To effectively target or transport the medication to the site of disease, recent development has been made in site-specific drug delivery to colon. These technologies involve the MMXTM technology, PHLORALTM technology, COLALTM technology, and CODESTM technology. These technologies are beneficial in overcoming the limitations of the existing approaches [79].

MMXTM Technology: This technology is known as multi-matrix technology. Diffusion-based release mechanism along with pH triggering system forms the basis of this technology to attain sustain release of a drug. However, rapid therapeutic action cannot be achieved through this technology. In this system, the external hydrophilic matrix is developed through in situ hydration of a selected chain of polymers containing the dispersion of drug in the internal lipophilic matrix. To delay the release of drug in stomach, a layer of pH-dependent, the gastric resistant film is applied. When this system reaches the colon, the fluid gets imbibed into the core of the system as the coat dissolves in the colon. As the fluid reaches the core, the formation of the thick gelling film occurs through which the drug disperse and release in the colonic site. In a study, a controlled release matrix tablet has been developed coated with a mixture of Eudragrit L and Eudragrit S. This tablet comprises of hydrophilic and lipophilic compounds as a

matrix in which the medication is incorporated. This tablet is beneficial for the treatment of ulcerative colitis as it has 1.2 gm of 5-Aminosalicylic acid. When the tablet enters gastrointestinal tract, hydrophilic matrix makes it swell in the course of time and formation of thick gelling film occur. Gel mass breaks off when it came in contact with the colonic anaerobic bacteria as it travels through colon, and drug is released [80].

PHLORALTM Technology: This is a novel technology in colon targeted formulation systems. The combination of pH-responsive mechanism and bacterially triggered mechanism forms the basis of this technology. This system consists of a blend of Eudragrit S (pH-responsive polymer) and resistant starch (biodegradable polysaccharide) in a monolayer matrix layer. The disintegration of the film in the upper gastrointestinal tract is restrained by pH-responsive polymer. A pH-responsive polymer is also responsible for controlling the swelling of starch.

The pancreas secretes the enzyme called mammalian amylase, which digests the coating. So, resistant starch is responsible for resisting the digestion by mammalian amylase but is quickly digested by microflora of the colon. Research of gamma scintigraphy reveals that this technology provides effective colon targeting. At the colonic site, consistent degradation of coated tablets was seen by gamma scintigraphy [81]. The precise release of drugs in the colonic site in both healthy and volunteers having diseased state was demonstrated by this technology [82].

CODESTM Technology: This technology was developed to prevent the existing limitations related to pH or time-based approaches [83]. The combined approach of pH-based or microbial triggered system forms the basis of CODES technology. This system consists of lactulose which triggers the release of medication from the formulation system to the site of colon. In this system, there is a tablet core which contains lactulose. This core is covered with Eudragrit E which is a acid soluble material [84]. Then this system is further coated with a layer of Eudragrit L which is an enteric material.

When the tablet passes through the GIT, the enteric coating do not allow the disintegration of the tablet when it is in stomach and then this layer of polymer dissolves readily following gastric emptying. When this tablet travels through the basic pH of the small intestine, the coating of acid-soluble material prevents the degradation of the tablet.

As soon as the tablet reaches colon, the colonic bacterial enzyme degrades lactulose into organic acids due to which pH in the microenvironment surrounding this formulation decreases resulting in the dissolution of the acid-soluble coating and subsequent release of drug [85].

A lower pH is required to dissolve the acid-soluble material layer because of the metabolization of lactulose to short-chain fatty acid [86, 87].

Pulsatile Technology:
Pulsatile Technology is Categorized into two Systems:

- **Pulsincap System:** Formulation in the form of the capsule is designed in this system. The drug release is controlled by placing the plugin in the capsule. In this capsule form, the active ingredient is the seal by using hydrogels which are swellable. As soon as the capsule reaches the dissolution fluid, it swells, and the plug gets displaced from the capsule after a lag time, and the drug is released. Various grades of the polymer are utilized as hydrogel plugs such as polyvinyl acetate, polymethyl methacrylate, hydroxyl propyl methylcellulose. The extent and junction of the plugin of the capsule body is responsible for controlling the lag time [88].

- **Port System:** Semipermeable membrane encloses the capsule body in this system. The capsule comprises of an insoluble plug containing osmotically active moiety and drug formulation. As soon as the capsule comes reaches the dissolution fluid, the pressure is developed inside the capsule body as the semi-permeable membrane allows the fluid to enter the capsule. This results in the drug release because of the expelling of the plug due to the development of pressure. With a time gap between successive periods, the drug is released at regular intervals [89].

Evaluation of Colon Targeted Drug Delivery System: Various *in-vitro*/*in-vivo* evaluation approaches have been introduced for assessing the

efficiency and stability of the developed colon-specific formulation.

A. *In-vitro* Evaluation: In *in-vitro* evaluation, the assessment of drug release is based on the ability of the polymeric film or coating to remain intact in the physiological environment of the stomach and small intestine. There is no availability of a standard evaluation method for assessing colon targeted system as an ideal *in-vitro* model should simulate an *in-vivo* state of gastrointestinal tract such as pH, volume, stirring, bacteria, enzymes, enzymatic activity, and a component of food. As these variations are affected by diet, physical stress so these factors makes it typical to develop a standard *in-vitro* model. *The in-vitro* model utilized for colon drug delivery are:

***In-vitro* Dissolution Study:** Dissolution of controlled or sustained release formulations for colon-targeted formulation system are generally complicated and the dissolution techniques described in the USP cannot fully simulate *in-vivo* conditions such as pH, bacterial environment and mixing forces [90]. The conventional basket method is used for carrying out the dissolution studies for colon-targeted formulations.

To assess the behavior of formulation at varying pH levels, parallel dissolution studies in different buffer solutions may be performed. Dissolution studies for colon targeted formulation in different media mimicking pH conditions likely to come across at different sites of gastrointestinal tract have been studied [91]. Different buffer media simulating the various parts of gastrointestinal tract were prepared, such as pH 1.2 0.1 N Hydrochloric acid to simulate gastric fluid, pH 6.8 to simulate intestinal fluid and pH 7.4 to simulate colonic fluid. Enteric-coated formulations for colonic drug delivery systems have been examined in a gradient dissolution test in three buffers. This formulation was tested for two hour at pH 1.2, then one hour at pH 6.8, and then at pH 7.4 [92]. *In-vitro* dissolution studies are carried out using USP dissolution apparatus type II in a different medium. O.1 N hydrochloric acid (pH 1.2) was prepared by adding 8.5 ml of concentrated hydrochloric acid to distilled water, and then the volume was made up to 1000 ml with distilled water. pH 6.8 phosphate buffer was prepared by dissolving 28.80 g of disodium hydrogen phosphate and 11.45 g of potassium hydrogen phosphate in water and then the volume was made up to 1000 ml. pH 7.4 phosphate buffer was prepared by dissolving 2.38 g of disodium phosphate and 8.0 g sodium chloride in water and then the volume was made up to 1000 ml. If required, pH of all prepared buffer solutions was adjusted by using calibrated pH meter [93]. pH 6.8 phosphate buffer with 4% w/v rat caecal contents was prepared by using male wistar rats weighing 105s-150 gm maintained on a normal diet. Thirty minutes before beginning the drug release studies, four rats were sacrificed by cervical dislocation. The abdomen was opened, the caecel contents were traced and immediately transferred to pH 6.8 phosphate buffer media [94]. *In-vitro* dissolution formulation assessment studies were carried out by using USP type II apparatus (Basket type) at 100 rpm for 2 h in 0.1 N hydrochloric acids (900 ml), than at pH 6.8 phosphate buffer media (900 ml) for 3 h and then finally at pH 7.4 phosphate buffer media for 3 h. Withdrawals of samples were done at regular time intervals, and then these samples were analyzed in a UV-Visible spectrophotometer.

***In-vitro* Enzymatic Studies:** [95]

This Study Categorize into 2 Types:

- The drug formulation is incubated in a fermenter having suitable media for bacteria. The total amount of release of the drug at varying time intervals was determined.
- Drug release study is executed in buffer medium containing enzymes such as dextranase, pectinase or rat, rabbit, guinea pig, cecal contents. The amount of drug release in a certain time is directly proportional to the degradation rate of polymer carrier.

B. *In-vivo* Studies: As various animals such as dogs, guinea pigs, pigs, and rats resemble the physiological conditions as well as micro-flora of human GIT, so they are generally used for assessing the delivery of the drug to the site of the colon. A relative model for the diseases related to the colon, such as inflammatory bowel diseases, should be considered while selecting a model for assessing a colon targeted formulation. The distribution of azo-reductase and glucouronidase activity in the GIT of rat and rabbit is fairly

comparable to that in the human [96]. A novel model has been proposed for rapid evaluation of colon-specific drug delivery systems. In this model, transplantation of human fetal bowel into a subcutaneous tunnel on the back of thymic nude mice was done, which vascularizes within 4 weeks and gains the ability to develop mucosal immune system from the host [97].

C. Gamma Scintigraphy: Gamma scintigraphy is a diagnostic examination where radioisotopes joined to the medication that travels to a certain part of the body and are taken internally, and the emitted gamma radiation is captured by the gamma camera to form a two-dimensional representation. This technique is based on the use of radioactive isotopes incorporated into the medicament so as to enable precise detection by a gamma-ray camera [98]. In a study, gamma scintigraphy was used to evaluate the efficacy of colon-specific tablets of tinidazole. Colon-specific formulation was radio-labeled by neutron activation. An isotropically enriched metastable isotope of technetium-99m was used. Tinidazole tablet, which is coated with guar gum and HPMC-K4M labeled with radioactive technetium-99m was ingested with 200 ml UV irradiated and filtered potable water by the subject. The gamma imaging was done at varying time intervals of 0, 1, 2, 3, 4, 5, 6, and 7 h using a gamma camera. The time at which the formulation passes the stomach (gastric emptying time) was found to be 2-3 h, and small intestine transit was found to be 3-5 h from the scintigraphic taken at regular time intervals. This study suggested that guar gum and HPMC-K4M coating over tinidazole core tablet prevents the release of drug in the stomach and small intestine, and medication is released when the formulation comes in contact with the colonic microflora [99].

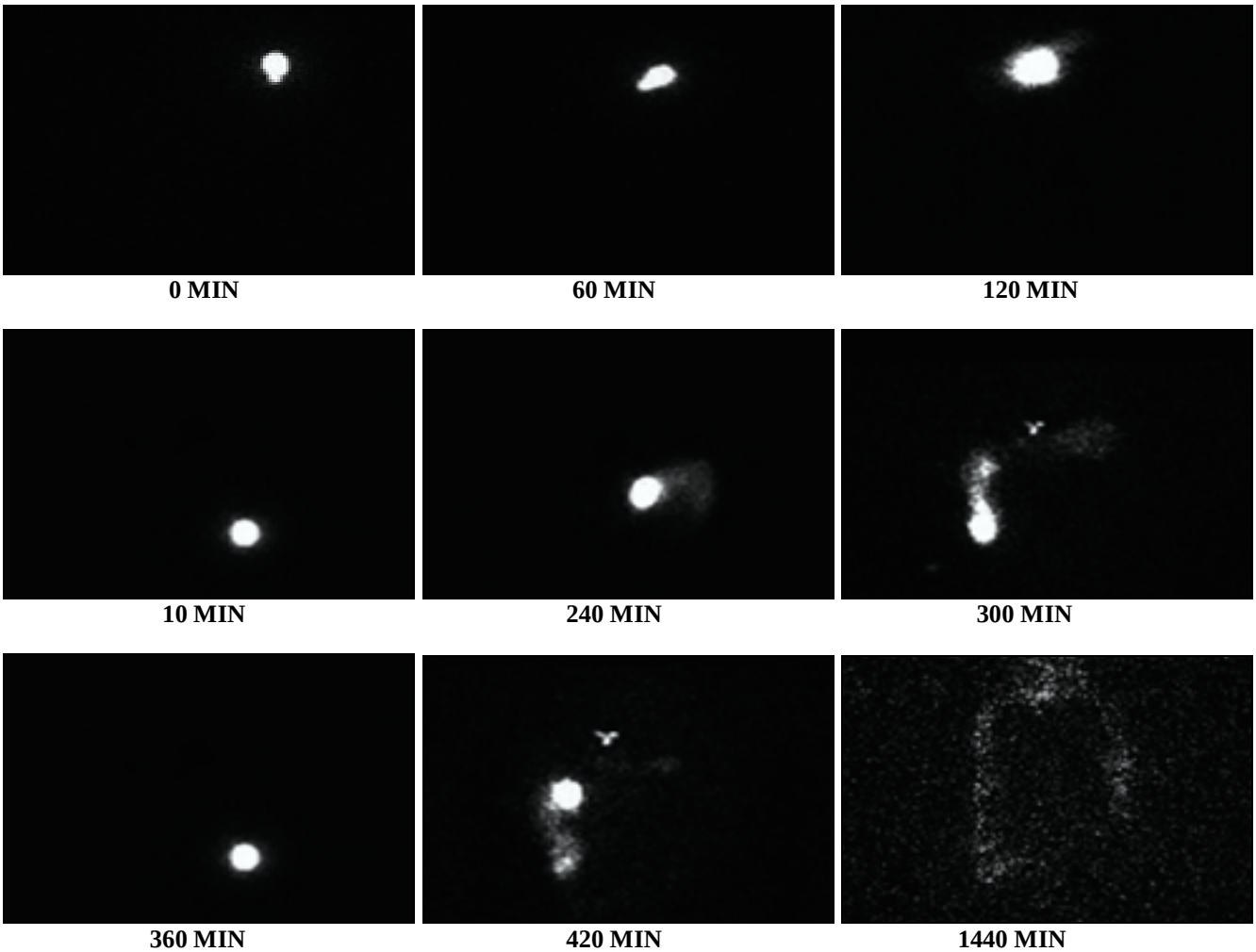

FIG. 2: SCINTIGRAPHIC IMAGES OF SUBJECT AFTER ORAL ADMINISTRATION OF 99MTC-LABELLED FORMULATION AT DIFFERENT TIME INTERVAL 99

Colon-specific Marketed Formulation [100, 101, 16]:

TABLE 4: COLON SPECIFIC MARKETED FORMULATIONS FOR ULCERATIVE COLITIS

S. no.	Marketed preparation	Drug	Dosage form
1	Asacol	Mesalazine	DR tablet
2	Mesacol	Mesalamine	DR tablet
3	SAZO	Sulphasalazine	DR tablet
4	Intazide	Balsalazide	Capsules
5	Dilacort	Prednisolone	Tablet
6	Lomotil	Diphenoxylate HCL, AtropeSuphate	Tablet

TABLE 5: COLON SPECIFIC MARKETED FORMULATIONS FOR CROHN'S DISEASE

S. no.	Marketed preparation	Drug	Dosage form
1	Pentasa	Sulphasalazine	TR tablets
2	Azulfidine EN	Prednisolone	DR tablets
3	Rayors	Budesonide	DR tablets
4	Colal-pred	Prednisolone	Oral colon targeted pellets
5	Flagyl ER	Metronidazole	ER tablets
6	Azasan	Azathioprine	IR tablets
7	Purinethol	Mercaptopurine	IR tablets
8	Gengraf	Cyclosporine	IR capsules, oral solution
9	Asacol	Mesalazine	DR tablets
10	SAZO	Sulphasalazine	DR tablets

TABLE 6: COLON SPECIFIC MARKETED FORMULATIONS FOR IRRITABLE BOWEL SYNDROME

S. no.	Marketed preparation	Drug	Dosage form
1	Normaxin	Clidinium bromide	Tablets, capsules
2	Pro-banthine	Propenthline bromide	Tablets
3	Colospa	Mebeverine	Tablets, capsules
4	Cyclominol	Diclomine	Tablets
5	Linzess	Linaclotide	IR capsules
6	Xifaxan	Rifaximin	IR tablets
7	Elavil	Amitriptyline	IR tablets
8	Amitiza	Lubiprostone	Soft gelatin IR capsules
9	Metamucil	Psyllium	IR capsules, oral powder
10	Citrucel	Methyl cellulose	IR tablets, oral powder
11	Bentyl	Dicyclomine	IR capsules, IR tablets
12	Imodium	Loperamide	IR capsules
13	Levbid	Hyoscyamine	ER tablets
14	Eldicet	Pinaverium bromide	Tablets

TABLE 7: COLON SPECIFIC MARKETED FORMULATIONS FOR DIVERTICULOSIS AND DIVERTICULITIS

S. no.	Marketed preparation	Drug	Dosage form
1	Asacol	Mesalazine	DR tablets
2	Xifaxan	Rifaximin	IR tablets
3	Citrucel	Methyl cellulose	IR tablets, oral powder
4	Metamucil	Psyllium	IR capsules, oral powder

TABLE 8: COLON SPECIFIC MARKETED FORMULATIONS FOR COLONIC AMOEBIASIS

S. no.	Marketed preparation	Drug	Dosage form
1	Flagyl ER	Metronidazole	ER tablets
2	Doryx	Doxycycline	DR tablets

Current and Future Scope: Nowadays, most of the researchers are focusing on the colonic site specific absorption of the drug for treatment of diseases mainly colonic cancer which requires highly specific absorption of drug. Targeting drug to the colonic site is one of the chief area on which the researchers are putting their efforts for maximum uptake of drug in optimum amount at the site of disease for treatment of colonic ailments. One of the major challenges is to improve the oral absorption of protein and peptide drugs as they are having less bioavailability because they are not

stable in the gastrointestinal tract. Thus, multi-particulate systems can be beneficial for the delivery of drug moieties such as oligonucleotides, protein, and peptides. So, these studies will be beneficial in the near future [102]. Three-dimensional (3D) printing technology is also being implemented in colon-specific delivery systems because of its significant role in personalized medicine. For the patient suffering from IBD, each patient requires personalized drug delivery, which can be addressed by 3D printing technology. This process involves layer-by-layer addition of active ingredient and excipient to design a particular structure in such a way to release the drug when coming in contact with the mucosa of colon [103].

The precision of colon targeting with the designing of novel *in-vitro* methods relevant to complicated *in-vivo* conditions will lead to the development of novel and innovative delivery systems. In the coming future, the mixture of novel and conventional systems is the key to design colon targeting systems as they improve efficiency, targetability, specificity, reduces cost, and increase patient compliance. For targeting the drug to the colon, the exploration of nanotechnology seems to be an area of research in the near future [104, 105, 106].

CONCLUSION: Colon-specific system requires a triggering mechanism that releases the drug from the formulation in response to the physiological condition of the colon (large intestine). Wide ranges of methods are available for colon targeted formulations, out of which polysaccharide system appear to be most promising. In terms of assessing the colon-specific system, there is a requirement of more advanced techniques for examining the release of drugs from the formulation apart from *in-vitro* studies. Colon-specific system has various therapeutic advantages in terms of treating the ailment locally or systematically. Colon targeting can be effectively achieved by using natural polymers that are easily degraded by bacterial enzymes of the colon. Research is going on in the area of colon targeting for the past two decades. From this review, it has been concluded that advanced approaches are more specific as compared to the existing approaches. Researchers are also working to develop more specific methods for assessing the colon targeted drug delivery system.

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