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Review Article

A REVIEW ON DEVELOPMENT OF COLON TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT

The purpose of this review was to select a promising drug delivery system for colon diseases. This review covers the development of Colon Targeted Drug Delivery System (CTDDS) using 36 y (1986-2022) data from various research and review articles. All fig. designed using by BioRender website. vThe colon-targeted drug delivery systems developed for the specific site drug delivery which applied for both local and systemic actions of the drug; since the drug targeted to be release within the colon, the unwanted systemic side effects are reduced along with it. Systemic side effects include organ damage, respiratory diseases and, cardiovascular damage and other illnesses. Colon-targeted drug delivery system used in the treatment of diseases in the colon, including ulcerative colitis, irritable bowel syndrome and colorectal cancer. The benefit of colon-targeted drug delivery besides the reduction of side effects also include protection from premature drug release or burst in the stomach or small intestine before reaching the colon. For the development of drugs with such benefits and advantages, drug delivery systems and approaches have used for Colon targeted drug delivery systems, varying from conventional colon-targeting drug delivery systems to novel approaches for Colon-targeted drug delivery systems. Conventional drug delivery includes the use of prodrugs, pH-dependent, time-dependent, matrix-based systems, polysaccharides-derived systems, and bio-adhesive system while novel approaches include types such as port system, pulsincap system, pressure-controlled system, osmotic controlled system, CODES, and the newest approach wish is the use of nanotechnology in colon targeted drug delivery. In this research both techniques reviewed, and their types discussed as well. The limitation of their uses and the advantage of each system discussed with a breakdown of the different mechanisms used to formulate such systems. A successful colon targeting delivery can release the drug to a specific segment in colon due to presence of different colonic enzymes formed by microorganisms that metabolize drug carrier linkage. Use of combined approaches i.e., conventional systems and newer approaches may be the best way to cure colon diseases using an optimized colon drug delivery system.

Keywords: Colon, Inflammatory bowel disease, Polymers, Colorectal, Cancer, Nanoparticles, Target, Drug delivery

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INTRODUCTION

Colon targeting drug delivery (CTDD) uses the administration of drugs in such a way that formulation passes the upper gastric system without any change in drug that disintegrates and absorbs in colon. There are gastrointestinal diseases where the local action of the drug is essential like Crohn's disease (CD), ulcerative colitis (UC), and irritable bowel syndrome (IBS). Metronidazole, prednisolone, sulfasalazine, hydrocortisone, and dexamethasone are medications used to treat these disorders [1, 2].

In colon-targeting drug delivery systems, there will be no loss of drug and the dosage reaches the targeted site with a higher concentration and less systemic side effects because the drug disintegrates and absorb in colon. Colonic mucosa enhances the absorption of drugs, especially peptides and proteins. The colonic contents have a long retention time up to 5 d, which makes the colon to be an ideal organ for the absorption of drugs [3]. There are two approaches for colon targeting, which are oral route and rectal route. While the oral one is most convenient and widely accepted by patients and a wide range of targeted formulations can be prepared via oral route, the rectal route is not the choice for the proximal part of colon as the drug cannot reach the exact targeted sites [4]. There are factors that affect the performance of colon targeting formulations like physio-chemical properties of the drug, type of delivery system, gastrointestinal transit time, and the interaction between the drug and gastrointestinal content. The efficient drug delivery to colon can achieved by ceasing the release of the drug or by protecting the drug release in the stomach and in the small intestine. This technique used to achieve a delayed drug release for prolonged time with lag time until formulation reaches to the colon [5]. Pharmaceutical formulations intended to use in colon targeting are mostly prepared in the form of solutions, foam, and suppositories [6]. The foam and suppository kept in the rectum and sigmoid colon while enema (solutions) have greater spreading property [1]. Table (1) shows drugs and their dosage forms for various colon diseases as well as their route of absorption [6].

Drug absorption mechanism in colon

(CTDDS) designed to achieve desired and effective concentration of drug in colon as well as the formulation still is intact in the small intestine [7]. Mostly the drugs either follow transcellular pathways or paracellular pathways. In transcellular pathways, lipophilic drug molecules travel through a path by permeating the cell surfaces. In the paracellular pathway, the hydrophilic drugs passed in between junction of cells. A fraction of drug absorbed in the small intestine due to the presence of a well-defined villi which is lacking by the colonic mucosa. The presence of this villi enhances drug absorption in the small intestine whilst the lack of this villi marks the large intestine not ideal for drug absorption through conventional formulations; hence the need for colon-targeted drug delivery systems to better enhance drug absorption [8]. Although drug absorptions occur primarily in the small intestine due to the colonic mucosa having a tighter epithelium, which contributes to its lower paracellular permeability as well as a higher electrical resistance of the epithelium of colonic mucosal when compared to the small intestine [9]. The lower transit time of the colon allows the drugs to stay longer in colon by increasing the duration of time that they stay in contact with colonic mucosa, in addition, the content in the colon is more viscous causing a slower dissolution rate, thereby making the diffusion of drugs through the colon also slower. These properties change according to the length and the fluid content of the colon. In theory, drugs absorbed throughout the entire GIT; however, commonly the drugs absorbed in the duodenum and proximal jejunum of the small intestine [8]. The delayed-release dosage forms designed to achieve an effective drug release in colon. This colon-targeted formulation shows a “burst release,” a sustained or a prolonged release, or a targeted release. Two main categories of colon targeted drug formulations are single unit colon targeted drug delivery system and multi-particulate dosage form systems. The disadvantage of single unit CTDDS considers the formulation inadequate. Such disadvantages include unintentional disintegration, which can be due to improper manufacturing process or due to the uncommon physiology of the GI [8], including non-disease dependent factors like age (pediatrics and

geriatrics), ethnicity, genetic factors, obesity and pregnancy as well as gastrointestinal tract (GIT) diseases which all lead to altered bioavailability of the drug in the colon [10]. The multi-particulate dosage form systems are the more common formulations due to certain properties like better bioavailability, reduced toxicity, reduced risk of local irritation and predictable gastric emptying [8]. Table 2 showed the different drug preparations and their benefits in treatment of different diseases in the colon [11]. Fig. 1 and 2 illustrated the type of cell in the colonic crypt and the absorption pathways in the colon, respectively.

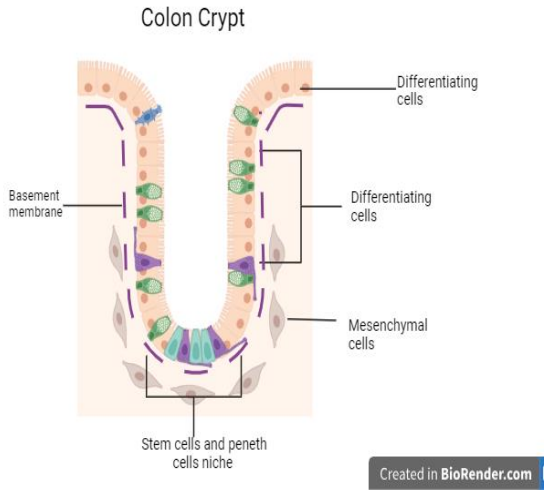

Fig. 1: Colonic crypt and the types of cells [12-14]

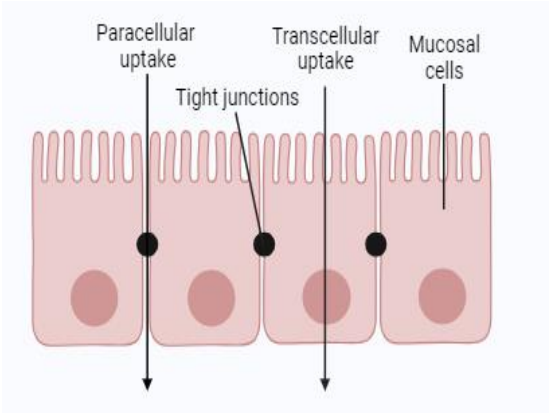

Fig. 2: Drug uptake pathways in the cell [15, 16]

Table 1: Drug used for colon targeting

Drug	Indication	Dosage Form	Absorption	Source
Bisacodyl	Constipation	Suppository, Enema	Local	[6]
Glycerol	Constipation	Suppository	Local	[1, 6]
Saline laxatives	Bowel preparation	Enema	Local	[6]
Mesalazine	Inflammatory bowel disease	Suppository, Enema, Rectal Foam	Local	[1, 6]
Budesonide	Anti-inflammatory	Rectal foam	Local	[1, 6]
Prednisolone	Anti-inflammatory	Rectal foam	Local	[6]
Hydrocortisone	Anti-inflammatory	Suppository, Enema	Local	[6]
Polystyrene sulfonate resins	Hyperkalemia	Enema	Local	[1, 4, 6]
Glyceryl trinitrate	Anal fissure, hemorrhoids	Ointment	Local	[1, 4, 6]
Acetaminophen	Pain, fever	Suppository	Systemic	[1, 4, 6]
Oxycodone	Pain	Suppository	Systemic	[6]
Ondansetron	Nausea and vomiting	Suppository	Systemic	[1, 6]
Caffeine+ergotamine	Migraine	Suppository	Systemic	[6]
Prochlorperazine	Nausea and vomiting	Suppository	Systemic	
Promethazine	Antihistamine	Suppository	Systemic	[1, 6]
Ibuprofen	Pain, fever	Suppository	Systemic	[6]
Diclofenac	Pain, fever	Suppository	Systemic	[6]
Indomethacin	Pain	Suppository	Systemic	
Diazepam	Seizures, sedation	Enema, Gel	Systemic	[6]

Table 2: Different drug preparations and their benefits in treatment of different colon diseases

Preparations	Their benefits in treatment of diseases in colon	Source
Oral Preparations	Localized treatment of diseases and conditions such as inflammatory bowel diseases, irritable bowel syndrome and colon cancer mainly as well as others. They can also put for use in the chronotherapy of diseases which affected by circadian biorhythms, such as asthma, hypertension, and arthritis.	[11]
Topical Preparations (foams, suppositories, or enemas)	They play a key role in the treatment of ulcerative colitis, either alone or while combined with oral steroids.	[11]
Old Systemic and Topical Steroids Preparations	Synthetic glucocorticoids considered as the tradition corticosteroids used for the treatment of Ulcerative Colitis.	[11]

Advantages of colon targeted delivery system

CTTDS is an ideal route for the drugs that undergo degradation in stomach and small intestinal enzymes. It also protects the drug molecules from the first-pass effect mechanism and decrease systematic side effects of drugs by targeting the drug directly to the site of action [4].

Drug criteria for colon targeting delivery

The criteria include drugs that used to treat chronic colitis, ulcerative colitis, colorectal disease, and CD as well as drugs that have poor solubility in stomach and small intestine and drugs have local effects on the colon [1].

Limitations for colonic delivery system

Colon is in the distal part of the gastrointestinal tract. The first challenge in drug delivery is to make the orally administered dosage form pass into the stomach and small intestine without any release of its active ingredients. The second challenge is the complex GIT physiological factors like pH of gastric content, fluid volume, resident and transit time of formulation, and presence of metabolic enzymes and foods [2]. There is another factor related with the drug solubility, which is the pH of colon and viscosity of colonic content. Since the water absorbed in colon so the content of the colon becomes viscous to keeping the stability of the drug molecule in colonic media, due to the presence of colonic enzymes (bacterial flora) in colon [3].

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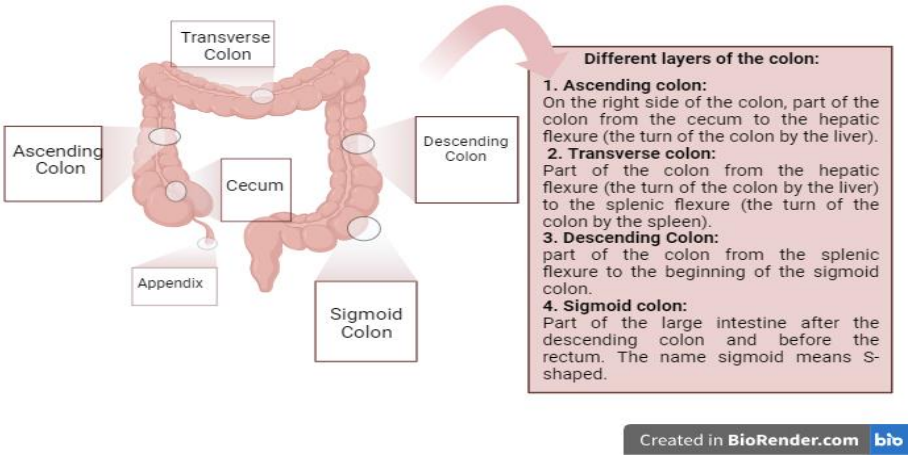

Fig. 3: Anatomical structure of the colon [17]

Colonic transient time

The normal transient time of colon affected in few cases such as in case of UC where the transient time decreased (24 h) as compared to normal person (52 h). The colonic transient time delayed during sleeping and changed in case of fed and fasting state. So, the colonic transient time is a crucial factor about the bioavailability of drugs in colon [4].

Colonic fluid volume

Approximately 90% of the water that enters the colon is absorbed. So, the colonic volume becomes low that leads to difficulty in drug dissolution from the dosage form. The undigested food (proteins, carbohydrates, fats) that enters in the colon is a substrate for the microbial flora (microbial enzymes) that so affect drug metabolism and absorption from colon [5].

Colonic luminal viscosity

The high-water absorbing ability of the colon turns the high viscosity of colonic content in lumen as compared to the upper gastrointestinal tract. The drug dissolution and drug absorption decrease with an increase in viscosity of lumen contents. The viscosity alters the penetration of drug molecules to the site of absorption or the disease-causing bacteria in the colon [2].

Colonic enzymes

Colon consists of over four hundred different aerobic and anaerobic microorganism species, such as *Clostridium* and *Escherichia coli*. There are a variety of hydrolytic and reductive enzymes produced by these microorganisms that metabolize the xenobiotic, deactivate metabolites and protein fermentations. Drugs are also susceptible to colonic enzymes and because of the metabolism, there may be formation of either active or inactive metabolic products [24].

Formulation forms

There are various methods to prepare and formulate the colon targeting delivery systems. The formulation factors like dose and physicochemical properties of the drug affect the bioavailability and marketability of drug delivery systems in colon [1].

Approaches used in colon targeting drug delivery system

Primary approaches

Azo polymeric prodrugs

Prodrugs are the inactive drug molecules administered in body like Aspirin (Salicylic Acid), Psilocybin (Psilocin), Irinotecan (SN-38), Codeine (Morphine), L-Dopa (Dopamine), Prontosil (Sulfanilamide), Cyclophosphamide (Phosphoramide Mustard), Diazepam (Oxazepam), and Enalapril (Enalaprilat). They convert into active form on hydrolysis by enzymes such as Xanthine oxidase reductase converts allopurinol to oxypurinol, butylcholinesterase converts bambuterol to salbutamol, hepatic esterase converts enalapril to enalaprilat, nitro reductase converts CB1954 to its activated cytotoxic form 5-aziridin-1-yl-4-hydroxylamino-2-nitrobenzamide, sulfoxide reductase converts Sulindac to its active form sulindac sulfide, β-glucuronidase (β-gus) converts DOX-GA3 to Doxorubicin [25]. Fig. 4 stands for the schematic diagram of enzyme degradation in the colon. The azo bond of salicylazosulfapyridine (SAS) is divided and there is the release of 5-aminosalicylic acid (5-ASA) and sulfapyridine in the colon [20]. Fig. 5 showed the hydrolysis of sulfasalazine. The success of colon targeting depends on minimum hydrolysis of drugs in the upper GIT while maximum hydrolysis needed in colon to achieve improved bioavailability [1, 21]. These polymers used as drug carriers. Two types of polymers used in colon targeting: synthetic and natural polymers. Although the drug molecule and the polymer joined by azo linkage, not considered a flexible method as the azo linkage depends on the functional group of the drug molecule. In azo polymers the high colon-specific activity achieved due to the addition of pH-sensitive monomers and azo cross-linking agents in the hydrogel structure. The swelling capacity of the polymers increases as the pH increases within the GIT, eventually when the polymers arrive in the colon, they have swelled to a degree that the azo cross-linking agents become accessible to the azo reductase enzyme present which leads to later degradation of the drug [2]. The second method includes the addition of the hydrolysable moieties in the hydrogel structure of the drug [22]. The azo conjugates are the most exploited groups to prepare the azo polymeric prodrugs [23]. The metronidazole is formulated as a prodrug that shows no systemic absorption and not metabolized in the small intestine. In another study conducted by Jung *et al.* and Kim *et al.* the sulfate group used to prepare metronidazole as a prodrug [24]. The formulation showed no chemical change and remained intact in the upper gastrointestinal tract and metabolized in the colon. Even a minimal amount showed systemic absorption [25]. Azo bond conjugates often used for the treatment of IBD. The prodrug used for colon-targeted drug delivery is 5-Amino salicylic Acid (5-ASA) prodrug; the amount of sulfasalazine reaching the colon unabsorbed is 85% which then undergoes reduction due to the anaerobic environment of the stomach [24]. Both *in vivo* and *in vitro* studies showed the successful delivery of drug and pectin conjugation in the colon with no change. There was no drug release in acidic media (stomach) as a result, the drug delivered to the targeted place, colon. There is another technique to protect the drug molecule from the degradation in stomach and small intestine, which is by binding the drug to a carrier via a covalent bond-like drug molecule linked with carrier (cyclodextrin, dextran, amino acid) using azo bond.

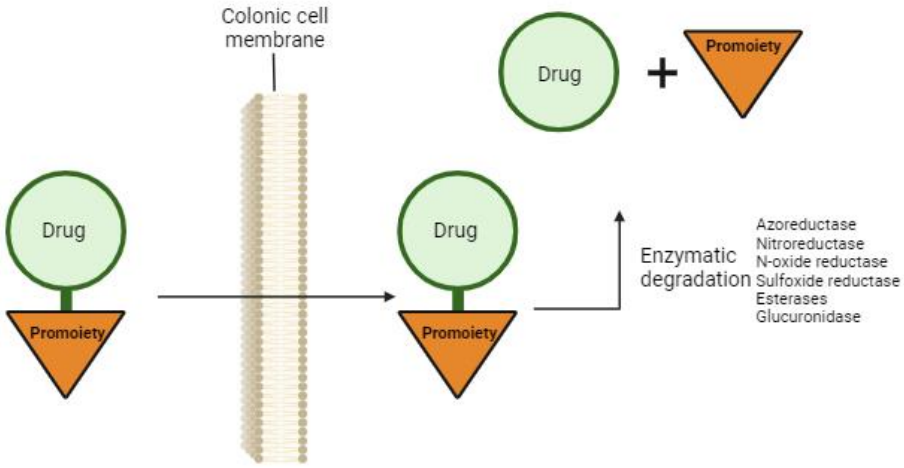

Fig. 4: Enzymes degrading prodrugs to active metabolites in the colon [26]

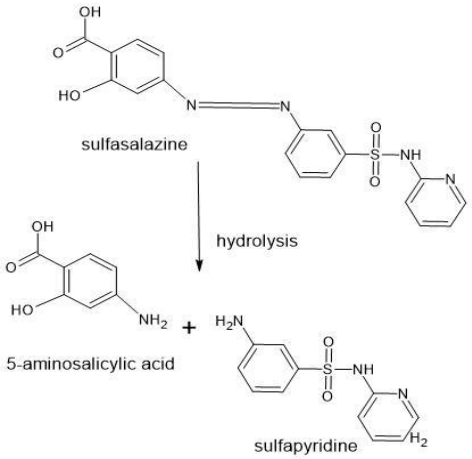

Fig. 5: Hydrolysis of sulfasalazine [27]

Colon-specific biodegradable delivery system

Colon consists of various kinds of microflora (aerobic and anaerobic bacteria) such as *Bacteroids, Eubacteria, Clostridia, Enterococci* and *Enterobacteriaceae*. These microflorae obtain their energy by fermentation of undigested substrates. Enzymes like glucuronidase, xylosidase, nitro reductase, and azo reductase formed in the colon [4]. Use of these enzymes is a good approach for colon targeting delivery [28]. Polymers used as a carrier for the drug molecule to formulate the CTDDS. These delivery systems may undergo chemical modifications and degradation by colonic enzymes [24]. Azo-aromatic polymers are the most explored groups for colon targeting. Hita *et al.* [29] suggested that these drug carriers protected from peptidase enzymes in the stomach and other enzymes in the small intestine, but they undergo degradation by azo-reductase enzyme only in the colon [30]. Various azo polymers used as coating material to cover the drug molecule in the core from metabolized and absorbed in the upper gastrointestinal tract [29]. These azo polymers cleaved by azo-reductase enzyme in the large intestine. When a drug, linked or coated with an azo-aromatic group, the azo linkage degraded by colonic enzymes and release of drug molecules takes place in colon [4].

Roos *et al.* [30] took the initiative in the synthesis of an acetyl derivative of guar gum which later used for the synthesis of a hydrogel of bovine serum albumin (BSA). It seen that as the degree of substitution increased which in turn decreased the rate of hydrolysis due to the side chain presence. However, once B-mannose added, it increased the release of BSA. This led to the use of azo-aromatic polymers for the CTDDS [31]. Another study conducted [32] in which two pellets one uncoated and one coated with polymers that triggered by bacteria seen. The latter one showed more specificity to the colon.

Matrix-based systems

The drug molecule embedded in polymer matrices and release of the drug takes place in the colon. These polymeric matrices can be pH sensitive or undergo degradation in the large intestine (colon). In case of pH sensitive polymeric matrices, the drug matrix combination is prepared in a way in which the matrices will degraded in basic pH of colon only. The studies showed controlled drug release based on pH [4,33]. One of the mechanisms for pH dependent matrices include extrusion/spheronization technique which uses uniform-size sturdy pellets to deliver the drug into the colon. It applied when the possibility of getting mechanically strong granules is not possible by other methods. Polymers such as Eudragit S100 (ES100) used as pH-dependent matrices in such a manner [34]. Polysaccharide used for such purposes include amylase, guar gum, pectin, chitosan, inulin, cyclodextrins, chondroitin sulphate, dextran, and locust bean gum. These polysaccharides are useful for use in pH-dependent matrices because they are inexpensive and nontoxic. They must turn into insoluble polysaccharides by crosslinking or hydrophobic derivatization [35]. Another study conducted by Bose *et al.* [36] which used the usage of two types of gum, kondagogu gum and ghatti gum in matrix-based colon-targeted drug delivery, concluded that both types of gum are natural and biodegradable polymers that can used as carriers in the development of colon targeted drug delivery. SK Vemula and colleagues [37] conducted research by using hydroxypropyl methylcellulose (HPMC) matrix-based formulation to deliver flurbiprofen to colon to treat inflammation and the result showed increased efficacy of the drug when used as a matrix-based colon-targeted delivery system. However, a major problem associated with pH-based matrices is their premature release in the small intestine before achieving colon-targeted drug delivery. Such drawbacks are related to the pH variations within the small intestine which differs from person to person as well as lack of coating materials appropriate for such usage [38]. Although polymers like Eudragit® L100 and Eudragit® S100 have used to overcome such problems which are known to be soluble at pH 6.0 and 7.0 or higher they are not suitable for releasing the drug the drug at a pH ideal for CTDD [33, 39]. The pH-dependent systems marked as less specific due to these minor variations between small intestine and colon since the mechanism of such formulation is through the release of the drug which consists of coating with enteric polymers that disintegrated once the formulation goes near the colon where the pH becomes alkaline [40]. Advantages of such systems include patient compliance, reduced dosage, and frequency of dosing [41].

Time-controlled release system

Time-controlled release systems or time-dependent systems are also known as pulsatile delayed or sigmoidal release systems [34]. The drug release in the colon can be reduce by achieving a sustained drug release pattern. Due to huge variations in gastric emptying time, it is difficult to predict the correct time at which the drug reaches the intestine, which results in poor availability of drugs in the colon. The gastric emptying time may be increase in case of irritable bowel syndrome. Drugs also affect gastrointestinal motility, transient time (food content) are disadvantages of this technique since the technique is transient time dependent [5]. To achieve the release of such drugs, estimation of lag time become essential. Lag time is the time needed for the transit of the drug from mouth to colon. Fig. 6 illustrates the different pH and lag time of organs in the human digestive tract. Gastric emptying time is variable, but it is constant in the small intestine or rather there is minimum variation. The lag time of the small intestine is usually 3-4hours, and a lag time of 5 h taken into consideration for colon. These formulations are ideal in cases where the patient needs the drug on need, or the drug required to be release at a pre-selected site in the GIT. However, time-dependent drug delivery also has problems like pH-dependent matrices in that there is variation with the GIT such as gastrointestinal movement, especially peristalsis, accelerated transit of the drug within different regions of the GIT as well as gastric emptying time; however minimal it is, causes problems for delivery of drugs through such systems. Overall, these variations differ from person to person, which makes it unpredictable [34]. The combination of this technique with the pH sensitive polymers enables the ease of colon targeting delivery system. A formulation having the drug core enclosed in polymeric layers consisting of a hydrophilic layer and two pH sensitive layers is a good example of this technique [4]. Such formulations can offer drug protection until the drug reaches into the small intestine avoiding the release of the active ingredient in the ileum using polymers with controlled release properties. Patel and his group did an experiment where they designed a drug formulation consisting of a combination of time and pH-dependent system to deliver mesalamine into the colon. This drug formulation consisted of three parts where mesalamine was in the innermost part of the tablet. Which then coated with a pH-dependent polymer like Hydroxymethylpropyl cellulose (HPMC) K4M and enteric-coated with Eudragit L100. The *in vitro* studies showed promised results [39].

Bio-adhesive systems

Polymers like polycarbophil, polyurethane, and polyethylene oxide used as bio-adhesive components that cause retention of formulation for a prolonged time in the colon to enhance absorption of poorly water-soluble drugs in colon [43, 44]. Different studies showed that the bio-adhesive microsphere has higher retention time in the colon as a result improved absorption. One *in vitro* drug release studies showed 10% of drug released in gastric, 25% of drug released in intestinal pH, while over 90% drug released at colonic pH [4]. when drug and bio-adhesive compounds combinations taken into consideration [45]. A study conducted [46] developed a rectal hydrogel having Tolmetin Sodium at the core and coated with mucoadhesive polymers. Different formulations of the hydrogel developed using different polymers such as hydroxypropylmethyl cellulose (HPMC), hydroxylethyl cellulose (HEC), carboxymethyl cellulose (CMC) and sodium alginate. This formulation allowed adhesion to the rectal mucosa and proved controlled release of the drug. The method of using mucoadhesive polymers can offer therapeutic advantages such as increasing the absorption of drugs. A candidate suggestion for such purpose is the use of acrylic acid polymers. This showed in a study by [47] in which they experimented; they delivered a mucoadhesive and a non-mucoadhesive polymer to the colon of a dog and saw their absorption through the InteliSite Companion device. The result of the study was in favor of the mucoadhesive polymer, which showed better colon retention time. Varum and his team through the usage of double-coating mucoadhesive system in the ileo-colonic in which

the mucus is thicker than the small intestine. A carbomer loaded pellet which formed through the extrusion–spheronization process resulting in a mucoadhesive and accelerated drug delivery. This formulation showed rapid dissolution of the carrier and prolonged drug release and disintegration. This is beneficial in increasing the colonic transit time often seen with such formulations [48]. Another study conducted by Liu and his colleagues showed a novel design for IBD treatment, using a mucoadhesive microsphere having anti-inflammatory properties and a shell having anti-acid properties. The overall formulation was a hydrogel consisting of the above characteristics formulating a thiolated-hyaluronic acid-alginate hydrogel (HA-SH-Ag) core which helped to increase gut immunity and had better colon-targeted drug delivery properties [49]. Fig. 6 proves.

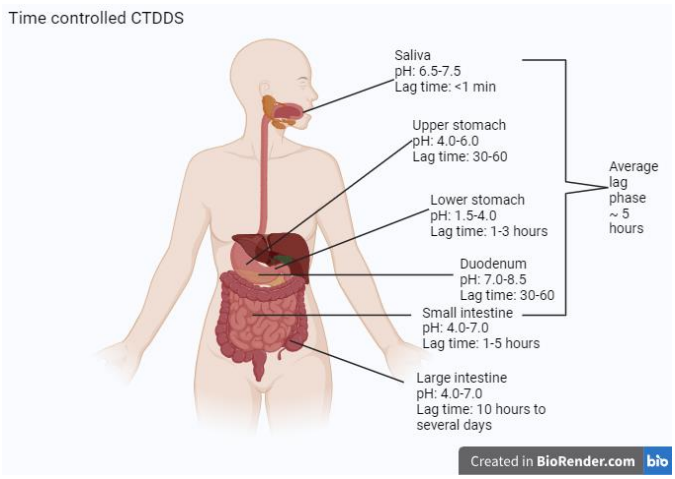

Fig. 6: pH and lag time of organs in the human body [42]

Polysaccharide–based delivery system

Polysaccharides are naturally occurring biodegradable compounds. They originated from animals (chitosan, chondroitin), and plants (guar gum, inulin) or microbial (dextran) [21]. These degraded by colonic microbial enzymes and so they are extremely attractive for colon-targeting delivery systems. In addition, they found in abundance, have a wide variety of structures, chemically changed easily, highly stable, safe, and biodegradable [50]. Combination of polysaccharides for colon targeting showed better results as compared to individual use of polysaccharide. Since cellulose is orally un-absorbable, the cellulose and its derivatives mostly used for colon targeting. There are two types of cellulose esters named: non-enteric cellulose esters and enteric cellulose esters. The non-enteric cellulose esters are insoluble in water and show pH dependent solubility. They are insoluble in acidic media but soluble alkaline pH. Their solubility in alkaline media depends on esterification. They used for insoluble permeable coatings. Polysaccharides such as chitosan, pectin, and chondroitin often used than others for colon-targeting delivery systems because of easily degradation by enzymes in the colon and are safe for organisms. They formulated in thin coating films to deliver the drug to the targeted regions/sites [51]. The polysaccharides employed in CTDDS, and their applications showed in table 2.

Table 3: Polysaccharides investigated for use in CTDDS

Polysaccharide	Source	Properties	References
Starch	Plant	Starch hydrolyzed readily by enzymes through the acetal link	[65]
Amylose	Plant	Amylose stays resistant to pancreatic α-amylase while degrading by the bacterial enzymes present in the colon.	[21, 50, 65]
Cellulose	Plant	Colonic bacteria can produce endo-as well as exo-enzymes due to the colon being an anaerobic environment. These form complexes that degrade cellulose to form carbohydrate nutrients.	[65]
Pectin	Plant	They are not suitable for CTDDS because they degraded by bacterial enzymes in the colon which highly produce water-soluble oligalactorunates.	[21, 50, 65, 67]
Inulin	Plant	The inulin has incorporated into Eudragit RS films for preparation of mixed films that resisted degradation in the upper GI tract but digested in the human fecal medium by the action of bifidobacteria and bacteroides.	[21, 50, 65, 67]
Locust bean gum	Plant	Cross-linked galactomannan leads to water-insoluble film forming product-showing degradation in colonic microflora.	[21, 50, 65]
Guar gum	Plant	Guar Gum shows degradation in the large intestine due the presence of microbial enzymes.	[21, 50, 65, 67]
Chondroitin sulfate	Animal	They used as digestive substrates by the bacteroid inhabitants of the large intestine, such as *Bacteroides thetaiotaomicron* and *B. ovatus*.	[21, 50, 65, 67]
Hyaluronic acid	Animal	As a microcapsule, it can used for targeted drug delivery.	[65, 67]
Chitosan	Animal	It should be susceptible to glycosidic hydrolysis by microbial enzymes in the colon because it has glycosidic linkages like those of other enzymatically depolymerized polysaccharides.	[21, 50, 51, 65, 67]
Dextran	Bacterial	Glucocorticoid-dextran ester prodrugs have been prepared and proved efficacious in delivering drugs to colon	[21, 50, 65, 67]
Cyclodextrins	Bacterial	They undergo fermentation in the colon in the presence of vast colonic microflora into small monosaccharide and thus absorbed from these regions.	[21, 50, 65]
Alginate	Algae	The alginate beads have the advantage of being non-toxic, and dried alginate beads re-swell in the presence of dissolution media and can function as controlled release systems.	[21, 50, 65, 67]
Scleroglucan (Sclg)	Fungal sources	They are resistant to hydrolysis and their solutions show an interesting rheological behavior that includes the viscosity stay constant, even at high ionic strength, up to pH 12 and 90 °C.	[65]

Colon targeting system by coatings

Methyl acrylic acid-based polymers or Eudragit used for colon targeting. In this technique, the drug coated using polymer, so the drug becomes protected from stomach acidic pH and the formulation shows delayed release pattern. The polymers degraded at basic pH of the large intestine and colon-targeted delivery achieved. Enteric polymers are insoluble at the stomach (acidic pH), but soluble at alkaline pH [4]. The polymeric combinations used widely are Eudragit L and Eudragit S. These are methyl acrylic acid-based polymers that used in combination with different ratios for coating of drugs. The solubility of these combinations varies depending on pH. A study conducted on human volunteers [54] utilized EudagritS to protect the drug core for colonic delivery and results showed that EudagritS is an excellent candidate for colon-targeted drug delivery. Enteric-coated formulations used in colon targeting drug delivery systems. Fig. 7 illustrates the mechanism of enteric-coated tablet.

Formulations with these coatings show prolonged action and supply extended drug release. It used in dry compression coating of tablets. The powder drug and excipient compressed that shows high stability and prevents complex formations. The lag phase is one important feature of these formulations. The lag phase is the period from the administration of drug formulation to until the start of drug release. Pulsatile formulations are time-dependent dosage forms where the drug release is depending on the environmental condition of the gastrointestinal tract i.e., pH. The pulsatile formulation composed of different film coatings compositions bear different properties like rupturable, permeable, and semi-permeable layers. In rupturable layer formulations, the drug release takes place after an increase in hydrostatic pressure in the core that results in water flux through permeable polymer membranes or coatings, leading to the swelling of the water-permeable polymers, resulting in disruption of this coating layer.

The permeable layer or coating allows water to enter and mix with core to convert solid into liquid phase. The dissolved drug then exerts the hydrostatic pressure inside. As the polymeric layer dissolved, the drug release took place. Certain time is needed for the drug release and, termed as lag phase. The hydrostatic pressure increases because of water entry or inside water flux. When hydrostatic pressure exceeds the osmotic pressure cause drug solution to pumped out from the openings that designed in the formulation [1, 55].

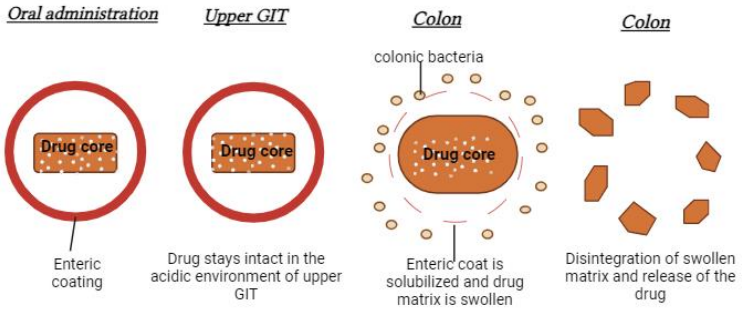

Fig. 7: Mechanism of enteric-coated formulation [56]

B-newly developed approaches for colon targeting

There are certain recent approaches for colon-targeting drug delivery systems. These techniques exploit physiological factors like luminal pressure and osmotic pressure [4].

Pressure-controlled delivery system

Colon content is more viscous than small intestine due to higher water reabsorption in the colon. The peristaltic movement of the colon is much more than that in the small intestine that results in increased motion in the luminal pressure at the colon. A study was performed by [57] on the development of ethyl cellulose (EC) polymers-based pressure-controlled delivery system capsules. The disintegration of the capsule was dependent on the thickness of the ethyl cellulose (EC) capsule, size and density and the drug release occur on disintegration and turned into liquid, but the colonic content is highly viscous than small intestine, so may be an obstacle for site-specific action [58].

The action of such formulation depends on the peristaltic movement of the stomach. This movement causes the breakdown of larger molecules to smaller ones and further transferred to the small intestine. And the peristaltic motion present in the small intestine moves these particles in a bolus action from one part of the GIT to another. Mass peristaltic movement in the colon which transfers the molecules or particles in the ascending colon to the transverse colon. Such movements occur only in specified amounts or times, sometimes three times a day, or four times a day. The result of these movements is an increase in the luminal pressure. Studies have taken advantage of such an increase in the luminal pressure in the development of pressure-controlled colon-targeted drug delivery [59].

For example, studies done by Amidon, S., J. E. Brown, and V. S. Dave [4] used the pressure of the colon to produce a specific drug formulation targeted at the colon, which consisted of gelatin capsules withholding the drug inside coated with ethyl-cellulose polymers which is water insoluble in the inner part of the capsule. It traps the drug within and has a suppository base that made to dissolve at body temperature after administration. The thickness of the insoluble polymer, which is ethyl cellulose (EC) decides how much the capsule disintegrated. Rangari Nalanda, T. and K. Puranik Prashant [60] saw the mechanism of this formulation. The drug enters the small intestine where water of the fluid present in the small intestine is absorbed by the capsule, increasing the viscosity and in turn, increasing pressure in the capsule, which results in drug expulsion into the colon via colonic bacteria, which degrades the swollen coating.

Osmotic controlled delivery

The osmotic-controlled release oral delivery (ORO-CT) system can formulate either as a single osmotic unit or may incorporated with 5-6 push-pull units and each unit is about 4 mm in diameter encapsulated in a single gelatin capsule. Each push-pull unit has an osmotic push layer and a drug layer. These layers are surrounded by a semipermeable membrane. Once the formulation is administered or swallowed, the gelatin capsules dissolve and they dissolve in small intestinal pH, dissolution media or when water enters in the system. But there is a drug impermeable enteric coating that restricts the entry of water in acidic media of the stomach. However, once the system reaches a higher or alkaline pH of the small intestine, the capsule dissolves at once and dissolution media or water penetrates the formulation. On the entry of dissolution media or water into system (formulation) causes swelling and pushes the compartment, resulting in generation of force that expels the drug out from an orifice through the membrane near the drug layer in a rate that depends on the rate of water entry into the semipermeable membrane [1, 55]. Fig. 8 shows mechanism of ORO-CT.

In the treatment of (UC), the compartments are designed in intervals of three to four hours post gastric delay for the prevention of drug delivery into the small intestine, in which the delay lasts until the

drug has been delivered into the colon, where it is released in a constant rate of 24 h or over a short period of 4 h [61].

A new developed phase transited system showed to be a good option in the use of formulations targeted at the colon. Philip and joint author show the performance of a drug that does not disintegrate and has controlled release with a capsular system of asymmetrical membranes for flurbiprofen in which different formulation variables put under the test for their utility as a controlled release drug formulation. The results showed that the drug release was dependent on the osmotic pressure of the dissolution medium rather than pH [62].

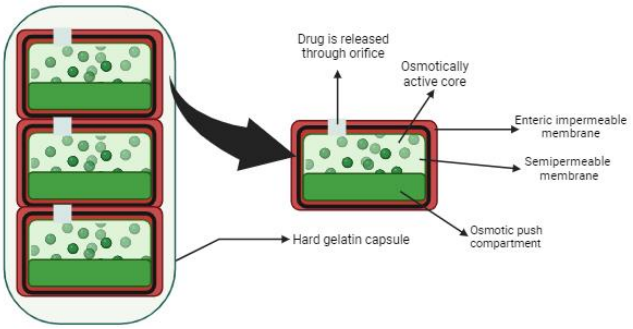

Fig. 8: Mechanism of ORO-CT drug delivery [63]

Pulsatile system

Pulsincap system

It is the combination of both a time-dependent released system and a pH-sensitive technique. Time-dependent systems are not suitable to use for colon targeting delivery alone due to change in gastric emptying time, variations in gastrointestinal transit due to peristalsis change and other colonic disorders such as irritable bowel syndrome (IBS). The Pulsincap system is composed of a water insoluble capsule body having the drug [1].

The hydrogen plugs are composed of materials like hydroxy-propyl-methylcellulose (HPMC), poly methyl methacrylate (PMMA) and polyvinyl acetate (PVA) [64].

The opened end of the capsule body or capsule cap is water soluble and sealed with a hydrogel plug. The drug is protected from the acidic media (stomach) by acid-insoluble film layer coating [1]. The enteric coat layer dissolves and the hydrogel plug swells on entry of formulation of the small intestine. The swelling of hydrogel plug in the small intestine allows for a lag time and handles prolong drug release in the colon. The lag time depends on the length of the plug and its extent of insertion [4, 55]. Fig. 9 illustrates the mechanism of the pulsincap drug delivery system. Selection of ideal polymer for the plug studied by Abraham, S., and M. Srinath [65] for the Pulsincap system. In the first five hours the formulation showed zero order drug release from the conduct of the experiment.

Port system

For the formulation of port systems, the capsule enclosed within a semipermeable membrane [64]. It consists of a gelatin case that has semipermeable membranes such as cellulose acetic acid derivativities [67]. The capsule contents made of a plug that is insoluble that has the active ingredient and the formulations of the drug. The capsule releases the drug when the pressure of the capsule increases due to contact with the dissolution fluid. The semipermeable membrane allows the entrance of the fluid into the body of the capsule resulting in the expulsion of the drug. The release of the contents of the capsule occurs at consecutive intervals with specific time intermission in between each interval [64]. Fig. 10 illustrates the mechanism of port system drug delivery. The time of the release can control through covering with different thickness as studied by Tiong, N. and A. A. Elkordy [68] through *in vitro* studies on naproxen having tablets coated with different liquid vehicles. The advantage of the use of such system is the avoidance of second-time dosing; Bansal D., *et al.* [69] developed liposomes that were trapped within alginate beads for the treatment of CRC, capsules containing Oxaliplatin (L-OHP) trapped within the alginate beads and coated with Eudragit S-100 and entrapped folinic acid coupled liposomes within the beads as well. The formulation used for *in vivo* drug delivery to the colon on mice and used for *in vitro* studies using a USP dissolution paddle type apparatus.

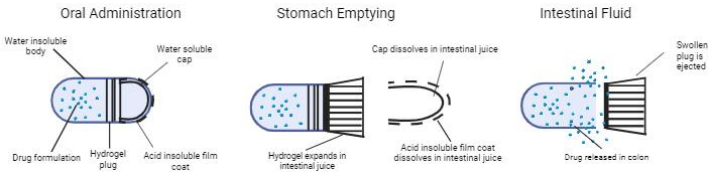

Fig. 9: Pulsincap drug formulation mechanism of action [66]

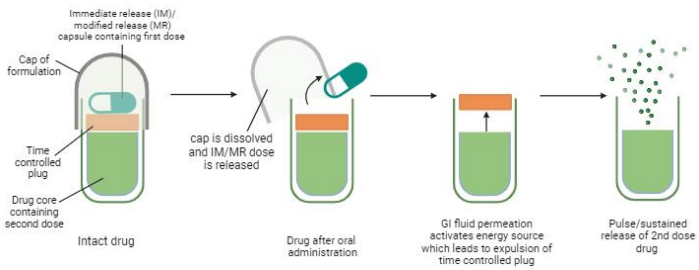

Fig. 10: Mechanism of action of port system drug delivery [70]

Newly developed CTDDS

CODES™

It is a budesonide pellet based on CODES ™ technology which is pH dependent and as well as a microbial-dependent combination system [71, 72]. This combination can overcome the problems that cause limitations of pH sensitive formulations and time-dependent systems (6). It consists of a lactulose-based core, acting as a trigger for site specific drug release in the colon. The core material coated using two different coating materials. The first coating is composed of an acid soluble material like Eudragit E and the second coating over the first coating consists of an enteric-coated material such as Eudragit L. [9]. The unique structure of CODES™ allows the drug to stay unaffected in the stomach due to the enteric coating; however, it dissolves rapidly after gastric emptying. The drug stays protected due to the presence of an acid-soluble coating. Coating dissolves in the small intestine. The pH of the small intestine is acidic, and the acidic coating of the formulation protects the release of the drug as it passes through the acidic pH of the small intestine. There is a small penetration of dissolution media and swelling of formulation in the small intestine. However, the polysaccharide (lactulose) is released in the colon and diffuses through the coverings due to the enzymatic degradation of the lactulose. It is degraded by the bacteria present in the colon, which converts lactulose to organic acid as represented in fig. 11. Such degradation alters the pH (lowering it) of the colon sufficiently for the acid soluble coating to dissolve and the drug released [6, 9, 60, 67].

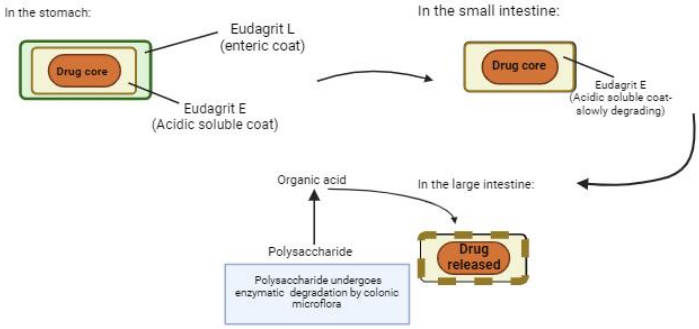

Fig. 11: Mechanism of CODES drug delivery [73]

Nanotechnology for colon targeted drug delivery

Nanotechnology has developed in colon targeted drug delivery to combat problems associated with the conventional formulations developed for CTDDS [74]. A reduction in size of the drug carriers enhances the permeability in the epithelial tissues which allows the accumulation of the drug in the diseased colon tissue. The reduction in the size to nanoparticles allows a better absorption of the drug by the immune cells that filled within the diseased tissue in the colon [75-77]. One specific formulation that is highly efficacious and reduces toxicities is employment of liposomes to deliver drugs which considered one of the most successful drug delivery systems which uses nanotechnology [78].

Another advantage of the nanoparticles is the surface chemistry associated with it since it enhances targeted drug delivery. The surface of nanoparticle-targeted drug delivery can conjugate with different targeting compounds including antibodies and ligands that specifically bind to antigens and receptors on the target cell surface, this allows for the drug to deliver directly to the specific cell and avoid off-target effects at the same time. These advantages allow for the use of nanotechnology drug delivery system which are novel drug delivery systems (NDDS) in the treatment of colonic diseases such as Colorectal Cancer (CRC) and (UC) [79, 80].

To achieve a highly efficacious colon targeted drug delivery in the form of nanoparticulate drug delivery system some challenges must be overcome, and these challenges include biological barriers, the differentiation of a tissue that has been contaminated with the disease from a tissue that is healthy, contain doses that are therapeutic of the active agent and most importantly it must target the colon only [81].

Dual-stimuli responsive (NDDS)

Some of the common CTDDS include pH-dependent, time released systems and microbial enzyme systems, however, these approaches have many complications such as site specificity for pH-dependent systems and can even cause pre drug release in the small intestine before reaching the colon and that make them less than ideal approaches for CTDDS. The pH-dependent nanoparticulate drug formulation in NDDS exhibited the same problem, releasing the drug at the pH of 7.4 at the ileum and failed at colon specific drug delivery assessed in animal colon [81, 82].

Time-dependent NDDS formulations had problems of their own as well including the release of the drug depending primarily on GI transit time which is susceptible to different variations due to food content, inter-individual variations, and delayed release [39, 83]. Hence time dependent NDDS formulation showed low site specificity and initial release due to a lack of pH sensitivity. This causes the release of the drug in the proximal GI tract which can lead to systemic absorption and side effects [82, 84]. Lastly, microbial enzyme dependent formulation is dependable however are associated with complications of their own including the inability to control drug release in the proximal GI tract like time-dependent formulation which is mostly due to them being mostly hydrophilic [85].

The above-mentioned problems are all associated with the systems being single-stimuli hence a dual-stimuli sensitive NDDS system has develop and various approaches fixated on formulations that can act in the same way as the mentioned above systems by combining them. Naeem in both his studies have developed systems that are a pH/time sensitive and enzyme/pH sensitive for colon targeting with the utilization of enzyme-sensitive polymers azopolyurethane and Eudragit® S100 as pH-sensitive polymers for the enzyme/pH dependent dual stimuli sensitive system and a polymeric mixture of Eudragit® FS30D as a pH-sensitive polymer, and PLGA as a time-dependent polymer for the formulation of pH/time dual stimuli sensitive system all by using nano-particulate formulations [86, 87]. The results of both formulations showed exceptional drug specificity and selectivity to colon which allowed adequate amounts of the drug to release at the correct location. This highly specificity allowed reduced systemic drug absorption and in result reduced the side effects caused along with it. The *in vivo* and *in vitro* studies opened a gateway for better drug delivery and further enhancement of each separate system by combining them in a dual stimuli-sensitive system through nanoparticle formulations, offer a promising result in the treatment of the diseases associated with colon specifically IBD and colitis [81].

Mucoadhesive and penetrating NDDS

The use of mucoadhesive in nanotechnology for NDDS increases the transit time of the GI tract through adhesion to the mucosal layers

within the tract. The mechanism of adherence includes the binding of the mucus to the nano-formulation through either the interaction of charged groups of mucin proteins with charged carrier particles resulting in the retention of the mucosal barrier or through hydrophobic interactions [88, 89].

A particularly important characteristic of NDDS is that their surface chemistry allows the alteration (increase or decrease) of adhesion to membranes or target-specific cells [90].

Shi, Chen, and Sim conducted studies that showed the adherence of catatonic nanotechnology drug delivery to the mucus present in the small intestine enhances the bioavailability of the drugs [91, 92].

Thus, this led to further studies by other researchers that suggested the benefit of cationic NDDS formulations can increase the property of adhesion within the mucoadhesive used in tissues with ulcerations in the colon which allows for their uptake by the inflammatory cells present in these tissues resulting a better therapy overall [93-95]. A study conducted [96] using harmine liposomes (HM-lip) having N-trimethyl chitosan (TMC) showed that this formulation has added benefits of protecting the drug in the colon as well as increasing the retention time in GIT and had higher bioavailability.

Oral formulations of colon targeted drug delivery are subjected to non-specific muco-adhesion in the proximal GI tract, which can lead to compromise in their specificity in drug delivery to the colon [81] suggested a method to overcome such problems by forming a shield to the cationic surface of the nano oral formulations that include the degradation of the shield through pH-sensitive stimuli at the colon while being protected at the upper GI tract. Lipid nanoparticles (LNP) covered budesonide and polyethyleneimine (PEI) were employed to make the formulation cationic in nature. The formulation was coat with Eudragit S100 (ES) to get anionic formulation, making overall an ES-PEI-LNPs. The ES layer removed due to being pH sensitive and the formulation changed from negative to positive in the colonic conditions after the removal of ES [97] conducted his study on mice and found that ES-PEI-LNPs avoided muco-adhesion in the upper GI tract specifically the proximal small intestine and the drug released and delivered to the colon tissues that had ulcerations through confocal analysis of tissue sections in the colon and bioimaging of the GI tract. Another problem associated with colon drug delivery is the side effect and efficient targeting and site specificity which can be overcome through sustained release of therapeutic doses of the drug to the mucosal layers, however, NDDS formulation have problems in penetrating due to the mucosal layers filled with epithelial tissue for protection which is counted as a major barrier [98-101] formed a test on inflamed small intestine through oral absorption of both formulations and saw their distribution into the ulcerated tissues showing equivalent results with PSNPs sticking to the lumen of the small intestine while the PEG-PSNPs showed distribution to the inflamed tissues.

Redox-responsive NDDS

This method was specifically useful in treatment of UC since during UC, overproduction of reactive oxygen species have seen in response to oxidative stress by the inflammatory cells of the ulcerated tissues [102, 103] Suggestions of the use of formulations that respond to redox changes can used in treatment strategies for CRC and UC has proven. Based on this, nanoparticles that can degraded by reactive oxygen species could release the drugs in the inflamed tissues [102, 103]. Based on [104] conducted his first study using redox nanoparticles (RNP) with nitroxide radicals acting as the reactive oxygen species acting within the core of the formulation, showed remarkable suppression of inflammation in the ulcerated tissues of mice with UC. A second study [105] used the same method on mice with UC colon cancer, showing remarkable suppression as well. However, problems such as premature drug release and instability are associated with RNPs despite considered as a novel approach for the treatment of CRC and UC [106, 107]. Naeem and his collaborators suggested the solution of using multiple stimuli-responsive NDDs to overcome such problems [81].

Targeted NDDS

During inflammation, immune cells express certain antigens or receptors, which can used in the formulation and development of a targeted drug delivery system through specific interactions. Active targeting of a diseased site proposed by surface functionalization of nano drug delivery systems using targeting ligands including folic acid (FA), hyaluronic acid (HA), lectin, mannose, and antibodies [108]. The mechanism of action is based on the ligands guiding NDDS towards the disease site after their administration by targeting cell surface receptors, protein or even adhesion molecules and this interaction will enhance the distribution and internalization of the nanoparticles within the disease site, this interaction is expected to increase the efficacy and targeted drug delivery through selective drug accumulation at the site while reducing the side effects associated with proximal GI tract premature drug release [109]. proposed the use of NDDS with active targeting with a formulation of aptamer-conjugated apigenin-loaded (Apt-ANPs) in poly lactic-co-glycolic acid (PLGA) NPs which put on the surface of the nanoparticles to target the biomarker responsible for adhesion in epithelial cells which found on CRC cell surfaces. And *in vivo* studies showed that the accumulation of the formulation in colon which reduced the risks associated with off-site cytotoxicity and enhanced the therapeutic efficacy. Utilizing hyaluronic acid functionalized PLGA NPs filled with tripeptides that were naturally occurring for targeted drug delivery in cases of UC, which showed reduction in the severity in experimental colitis, they engulfed by the epithelial cells and macrophages and accumulated in the diseased tissue [110].

Plant-derived edible nano-systems

Synthetic NDDS are associated with *in vivo* toxicity if used for long term and can be costly since it is manufacture only in large-scale quantities, which prove to be problematic and challenging [111]. However, the direct use of natural sources is less costly and do not have the above-mentioned challenges associated with the synthetic NPs, however,, they do have low solubility, absorption and bioavailability which can be challenging in their own way [112]. For this reason, the use of naturally derived nanoparticles for targeted drug delivery is a way to overcome the mentioned problems associated with their direct use, which will improve their therapeutic and physicochemical properties [113, 114] has recently proposed that ginger, grapes, grapefruits, carrots, and tomatoes can used for formulations of natural based nanoparticles through eco-friendly techniques. Along with the plant-based agents used in NDDS it also should have bioactive agents such as miRNA, lipids and proteins that serve as an excellent choice for their therapeutic use. For example, a recent study by [115] conducted the use of ginger-derived edible nanoparticles with a size of approximately 230 nm as well as a negative charged surface of for the treatment as well as prevention of diseases such as IBD and CRC. The formulation consisted of the ginger along with lipids, proteins, and miRNA, it loaded with doxorubicin and conjugated with folic acid on the surface of the nanoparticles. The study results showed no toxicity in animal models while it reduced the severity of colitis and further improved intestinal healing as well as the prevention of the development of chronic colitis or CRC. This combination showed remarkable tumor suppression within the mice when compared with free form of doxorubicin [115].

Other studies by Deng and Ju researchers showed comparable results in treatment of colitis in mice by using grape exosome-like nanoparticles and broccoli nanoparticles, respectively [116, 117].

Nano-in-micro hybrid system (NPs-in-MPs)

One of the limitations of NDDS in the use of colon-targeting drug delivery is their unwanted burst in the small intestine or the stomach when administered orally before reaching the colon due to the harsh and hostile environment that GI tract has before the drug can safely and efficiently delivered to the colon [81]. Polymers such as poly lactic-co-glycolic acid (PLGA), Eudragit RS, or lipid-based systems that used for sustained release oral based colon targeted NDDS can be challenging due to their inconsistent nature of releasing the drug, which is characterized by high burst first release as a large bolus of the encapsulated drug release. As well as their adhesion to the mucosa in the GI and the premature release of the drug in the stomach all prove to be challenging and difficult for efficient colon-targeting delivery of drugs [82, 97, 118, 119]. A study by [120] proved the absorption of drugs in the small intestine by Peyer's patches when covered with polystyrene particles in the sizes

ranging from 500 nm-5 um as well as finding high concentration of the compound in the kidney's liver and brain of rats [120]. To overcome the mentioned problems a formulation consisting of nanoparticles (NPs) encapsulated within hydrogels of microparticles (MPs) formed and it called NPs-in-MPs drug delivery system combining the characteristics of both formulations into one drug formulation [121, 122]. Advantages of oral NPs-in-MPs system includes the protection of the NP encapsulated within the GI transit time and from premature drug release [81].

For this purpose, a recent study conducted by [123] used protein nanoparticles that were encapsulated within alginate/chitosan MPs for safe gastric passage and release within the colon in which they experimented in a murine colitis model were the protein nanoparticles were delivered to the epithelial cells in the small intestine hence reducing inflammatory scores and suggested the use of different therapeutic proteins, vaccines, or antibodies to the colon [123]. Another study conducted by [124] suggested the therapeutic benefits of a hybrid dual particulate system, which had two biomarkers: chitosan NPs in zein MPs for oral DNA delivery. The results of the study were positive in regards of safe and efficient oral delivery of DNA and future gene delivery with a better protection and a better-controlled release of the compounds [124].

Table 4: Shows a summary of the CTDDS and the drugs used via such systems as well as their mechanism

Colon-targeted drug delivery system	Drugs	Mechanism	Source
Azo Polymeric Prodrug	Peptide drugs Film coating with azo polymers	Given orally to cats and dogs through coating with styrene and 2-hydroxyethyl methacrylate crosslinked with divinylazobenzene, which degraded by azo reductase enzymes in the gut once arrived. Copolymers of 2-hydroxyethyl methacrylate and methyl methacrylate along with bis(methacryloylamino) azobenzene evaluated *in vivo* an *in vitro* and results showed bacterial degradation in the intestine.	[20, 125, 126]
Colon Specific Biodegradable Delivery System	Bovine serum albumin (BSA)	O-Acetyl-galactoglucomannan (AcGGM) hydrogels prepared by chemically changing the AcGGM by 2-hydroxyethyl methacrylate (HEMA) and evaluating their hydrolysis by treating with B-mannanase. Results showed that more HEMA substitution caused less bovine serum albumin (BSA) release and addition of B-mannanase increased BSA release.	[30]
Matrix Based Systems	Metronidazole (MTZ)	A bioadhesive microsphere (BAM) having metronidazole using Assam Bora rice starch as a polymer which evaluated *in vitro* and showed degradation in alkaline pH. And an *in vivo* study showed that MTZ stayed intact in the small intestine and released in the colon due to the microflora present there.	[45]
Time Controlled Release System	Mesalamine	A time and pH-dependent CTTDS. Having mesalamine ta the core and inner coated with hydroxypropyl methylcellulose (HPMC K4M) as a time-dependent factor and Eudragit® L100 as a pH-dependent factor. This formulation showed acidity resistance and time resistance in *in vitro* dissolution tests. It prevents drug release in the acidic environment of small intestine for up to 6 h.	[39]
Bio-adhesive Systems	InteliSite Companion device Prednisolone Thiolated-hyaluronic acid-alginate hydrogel	InteliSite Companion device having; Carbopol 980, d polycarbophil AA-1 and Ethylcellulose (EC) as polymers delivered by the device into dogs. The Carbopol 980 has a longer retention in the proximal colon compared to the other two polymers. Pellets of prednisolone with different carbomers, including Carbopol 971P, Carbopol 974P and Polycarbophil AA-1. Another pellet with double coating system used in which they coated with an inner layer of partially neutralized Eudragit® S and buffer salt and an outer coating of standard Eudragit® S. another pellet with a single coat of standard Eudragit® S, used for comparison purposes. *In vivo* studies showed a longer colonic residence time, overcoming the pass-through effect as well as better oral bioavailability. A system with an orally administrated core-shell microsphere for colon-targeted drug delivery. *In vivo* studies of the Ag hydrogel shell showed degradation and colon-targeting function along the mucoadhesive ability of the thiolated-hyaluronic acid hydrogel core, reducing systemic exposure and increasing local drug dwell time. *In vivo* and *in vitro* studies showed reduction in inflammation for IBD treatment.	[47-49]
Polysaccharide-Based Delivery System	Insulin	Chitosan capsules delivering insulin used for colon-targeted drug delivery via coating it with the enteric coating material hydroxypropyl methylcellulose phthalate and administering it orally. *In vitro* and *in vivo* studies showed promising results where chitosan degraded by the microflora in the colon.	[51]
Colon Targeting System by Coatings	Diltiazem Hydrochloride	Tablet formulations have natural polysaccharides such as chitosan and guar gum for the purpose of acting as carriers and the active ingredient being diltiazem. The tablets coated with two layers, inulin as the inner coat and shellac for the outer coating. *In vitro* studies showed that the tablets coated with these two layers had controlled release in the stomach and small intestine while they had a maximum release in the colon, revealing that tablets with polysaccharide as carrier coated with inulin and shellac had enhanced colon-targeted drug delivery.	[43]
Pressure Controlled Delivery System (PCC)	5-aminosalicylic acid (5-ASA), tegafur (FT)	PCC systems having 5-ASA as suspension FT as a solution. *In vitro* dissolution studies showed higher systemic availability of these drugs when compared to tablets coated with Eudragit S. The capsules showed a higher systemic delivery. *In vivo* studies with oral administration also done on beagle dogs.	[57]
Osmotic Controlled Delivery	Flurbiprofen (FLU)	Asymmetric membrane capsules prepared with fabricated glass. The effect of different formulation variables studied as well as differential scanning calorimetry (DSC) studies. The results showed the drug being independent on the pH but dependent on the osmotic pressure.	[62]
Pulsincap System	Metronidazole	Capsules treated with formaldehyde to preserve and metronidazole pellets were put into the capsule's shells and three different formulations were prepared containing polymers guar gum, hydroxypropyl methylcellulose (HPMC) 10K, carboxymethylcellulose sodium and sodium alginate at different concentrations and a coating of 5% cellulose acetate phthalate to prevent variable gastric emptying, *in vitro* studies showed no release in gastric fluid while releasing major portions of the drug into the colonic fluid.	[65]
Port System	Oxaliplatin (L-OHP)	Oxaliplatin (L-OHP) anticancer medication used in the treatment of colorectal cancer were trapped within capsules of alginate beads coated with Eudragit S 100 and used for colon-targeted drug delivery, *in vivo* studies on mice showed that the beads covered with Eudragit S 100 entered the colon approximately 5h after oral absorption and *in vitro* studies also showed potential targeting to the colon.	[69]
CODES	Lactulose	Tablet with lactulose at the core covered with coatings of Eudragit E, which is the dissolvable corrosive ingredient and Eudragit L, which is the polymer for enteric protection. This system protected in the stomach due to the enteric covering and disintegrated at pH above 6.	[67]
Dual-stimuli responsive NDDS	Budesonide Cyclosporin A	A dual system formulation containing budesonide and pH-sensitive polymer methacrylate and enzyme-sensitive azo-polyurethane for the treatment of colitis was developed and tested on rats with UC and	[86, 87]

Colon-targeted drug delivery system	Drugs	Mechanism	Source
		results showed that the formulation was able to selectively target the inflamed parts of the colon and no *in vivo* or *in vitro* toxicity was seen hence deeming the formulation safe and effective for CTDDS. A dual formulation enclosing cyclosporin and coated with polymers Eudragit® FS30D as a pH-sensitive polymer and poly (lactic-co-glycolic acid) (PLGA) as a sustained-release polymer and *in vivo* studies of mic showed remarkable colon-targeted drug delivery.	
Mucoadhesive and penetrating NDDS	Budesonide	A pH-triggered surface charge-reversal lipid nanoparticles (LNPs) was developed, which enclosed budesonide and Polyethyleneimine (PEI) in order to make the formulation cationic as well as Eudragit® S100 (ES) coated onto the PEI-LNP to get pH-triggered charge-reversal LNP formulating an ES-PEI-LNP formulation which changed from negative to positive under colonic conditions in the GIT of mice and results showed effective removal of the UC.	[97]
Redox-responsive NDDS	Nitroxide radical-containing nanoparticle (RNP(O)) RNP(O) and irinotecan	RNP(o) coated with a shell of polyethylene glycol evaluated on mice induced with UC and results showed a greater accumulation of the formulations within the inflamed tissues and low distribution to other tissues compared to low-molecular-weight 4-Hydroxy-TEMPO (TEMPOL) or mesalamine. Combination of RNP(O) and irinotecan evaluated for colitis colon cancer and tests showed no toxicity despite long-term oral administration and the combination led to enhanced chemotherapeutic activity.	[104, 105]
Targeted NDDS	Apigenin Lysine-proline-valine (KPV)	Development of an aptamer-conjugated apigenin-loaded nanoparticle (apt-ANP) , which was used in colorectal cancer targeting the cancer cell surface biomarker epithelial cell adhesion molecule (EpCAM), its introduced site specificity with negligible cytotoxicity to normal cells and prolonged retention of the formulation at the targeted sites allowing increased therapeutic activity and a promising formulation in the treatment of colorectal cancer. Formulations developed with KPV loaded into hyaluronic acid (HA) polymeric nanoparticles (NP) producing an HA-KPV-NP that showed to be nontoxic and compatible to the cells within the intestine and the formulation had an exceptional effect in UC by increasing healing and reducing inflammation of the affected cells. This formulation encapsulated within a hydrogel such as chitosan or alginate showed increased therapeutic activity, hence demeaning the formulation of a promising system for colon-targeted drug delivery.	[109, 110]
Plant-derived edible nano-systems	Edible ginger nanoparticles (GDNPs 2) Grape exosome-like nanoparticles (GELNs) Broccoli-derived nanoparticle (BDN)	GDNPs 2 consisted of elevated levels of lipids, few proteins, miRNAs, and enormous amounts of ginger bioactive constituents (6-gingerol and 6-shogaol). The formulation evaluated on mice with UC and results proved the GDNPs taken up by the intestinal epithelial cells (IECs) as well as macrophages. They also showed to be nontoxic, reducing acute colitis in mice models and increasing healing while preventing further development into chronic colitis as well, all proving to be a promising therapy in CTDD. GELN target intestinal stem cells, when evaluated on mice induced with colitis and coculturing of GELN with crypt or sorted $Lgr5^+$ stem cells showed improved organoid formation and results showed beside renewal tissue process showed the formulation being able to also take part in remodeling of the process in response to pathological triggers. BDN evaluated on three mice models targeting dendritic cells (DCs), they activated adenosine monophosphate-activated protein kinase (AMPK) within the DC, and they induced tolerant DCs. This showed results in preventing colitis within the models through the activation of AMPK.	[115-117]
Nano-in-micro hybrid system (NPs-in-MPs)	Salmonella effector enzyme (AVrA) NP Oral DNA	Protein nanoparticles encapsulated with microparticles that are entero-protective formed with chitosan and alginate that proved to release the drug in the small intestine and colon. AvrA NPs encapsulated in alginate and chitosan microparticles reduced inflammation within colitis induced in murine models and had site-specific drug delivery and having potential in CTDD. A hybrid-dual particulate delivery system formed with the use of zein (ZN) and chitosan (CS) to deliver oral DNA formulating a Chitosan-Zein Nano-in-Microparticles (CS-ZN-NIMs), the DNA covered with CS formulated a nanoparticle formulation and encapsulated within microparticles of ZN. *In vitro* and *in vivo* studies of the formulation showed the potential of the use of this system for CTDDS.	[123, 124]

Evaluations of CTDDS

Various *in vitro* and *in vivo* techniques used to evaluate CTDDS [7]. The *in vitro* studies are more difficult to buy as the conditions and physiology of the stomach not easily recreated *in vitro* due to the influence of factors on the GIT. Hence *in vitro* models should inhabit the same conditions and factors as present *in vivo* such as pH, volume, stirring, bacteria, enzymes, enzyme activity, and other components of food. These factors also influenced by diet and physical stress [67]. The evaluation parameters of CTDDS are of two types.

***In vitro* evaluations**

Generally, depending on type of formulation, the evaluation varies like whether the formulation is pH dependent system or system degraded by bacterial microflora [127].

Dissolution test: The release of drug form controlled-release formulations is a complex mechanism. The description of the method as per USP is difficult to mimic the *in vivo* conditions using the basket-type dissolution apparatus. The drug release can study at various buffer solutions at different ph. For example, a solution of pH 1.2 used to simulate gastric fluid, pH 6.8 to simulate the jejunal segment of the small intestine, and pH 7.2 to simulate the ileum part of the small intestine. Meanwhile, enteric-coated formulations can evaluate using three different buffers, each for a specific time. For example: these formulations evaluated for two hours at pH 1.2, followed by one hour at pH 6.8, and then at pH 7.4 for 2 h in 0.1 N HCl of pH 1.2 as well as Sorensen's or Phosphate buffer of pH 7.4. The formulation should release its content when the pH is 6.8 which is the colonic pH.

Enzymatic tests: It involves the incubation of a carrier drug system with a proper medium for bacteria, including *Streptococcus faccium* and *Streptococcus ovis* present in the fermenter. The drug release measured at different time intervals or predetermined time intervals in alkaline buffer solutions having enzymes such as enzyme pectinase, dextranase or with guinea pig/rabbit rectal contents. In addition, fecal madeira of rat also used as it has colonic bacteria as it shows enzymatic induction even after 7 d. The rate of degradation of the polymer is proportional to amount of the drug release at the specified time [67, 127].

***In vivo* evaluations**

Animals like dogs, guinea pigs, rats, and pigs that have similar anatomic, physiological and microflora of the human gut used to evaluate CTDDS. Guinea pigs are the most widely used animal model for IBD. Rats and rabbits have azo-reductase and glucuronidase activity in the GIT that resemble with humans [8, 127].

a) String technique: A tablet attached to a string and allowed to swallow but leaving the string outside of the mouth. The string removed to examine the disintegration of tablet at different time intervals. Another method used to follow this technique is swallowing the tablet with induction of vomit in the subject [127].

b) Endoscope technique: The model injected with the drug and a gastroscope used to view the disintegration of tablet at once. A sedative administered to allow for the endoscope to swallowed [127].

c) Roentgenography: A radio-opaque material like barium sulphate incorporated in the solid dosage form and viewed by x-ray to detect the movement of formulation as well as the disintegration of the drug after oral administration [127].

d) Radiotelemetry: The effect of changes in the pH on disintegration of formulation captured by the insertion of a pH probe having capsule into the body [127].

e) Drug Delivery Index (DDI) and Clinical Evaluation of Colon-Specific Drug Delivery: This is a pharmacokinetic (PK) parameter used to measure the DDI of colon prodrugs. It considered as the ratio of relative colonic tissue introduction to the medication to the relative measure of medication in blood for example that is relative fundamental exposal to the medication. A higher DDI indicated better medication transportation [67].

f) γ–Scintigraphy: It is an imaging model to visualize the activity of drug delivery without being an invasive method [67] using a 99m-Tc DTPA tracer the process performed on guar gum matrix tablets. It followed by scintigraphy taken at various time intervals of the tablet for qualitative evaluations, however, it has disadvantages like the need of professional, qualified personnel and being an overall expensive procedure [67, 127].

Prospects in colon-targeted drug delivery

Colon-targeted drug delivery widely well examined by scientists over the past decades and accepted. They are also considered for treatment of colonic diseases locally and avoiding systemic effects of drugs, inconvenient as well as painful trans colonic administration of drugs. Another prospect can be the systemic delivery of proteins and peptides that readily degraded and poorly absorbed by the small intestine. CTDDS can possibility used for treatment of diseases that are related to the circadian rhythm, including asthma, angina, and arthritis. CTDDS can lead to better, rapid, and urgent delivery of drugs that absorbed by the colon and reducing their dose, such as steroids CTDDS can also be used for treatment of disorders that are specific to the colon where it is a necessity to reach an increased concentration of the drug, including irritable bowel syndrome (IBS), colitis, Crohn's disease, and other colon diseases. However, further studies needed for development of improved delivery and bioavailability of peptides and protein drugs based on oral dosage forms in the colon. More studies for the development of colon specific drug delivery are necessary for the improvement of CTDDS [8].

CONCLUSION

Colon targeting drug delivery systems allows both systematic and local action of the drug molecule, supplying therapeutic benefits for patient's safety, efficacy, and decreasing systemic side effects. Choice of suitable technique for colon targeting depends on varied factors such as type of formulation, physiological properties of the gastrointestinal tract, and physicochemical factors and these factors may be challenging to controlled for colon targeting drug delivery systems. A successful colon targeting delivery can obtained by preventing drug release and absorption in upper gastrointestinal tract by various technique that explained above and releasing the drug to colon, and the different colonic enzymes that formed by microorganisms help in releasing the drug particle and metabolizing the drug carrier linkage. It is better to combine both conventional systems and newer approaches to develop a good colon drug delivery system, but for future research for colon targeting drug delivery, the exploration of nanotechnology studies seems a field for the new technique developments.

ABBREVIATIONS

CTDD: Colon targeting drug delivery, CD: Crohn's disease, UC: Ulcerative colitis, IBS: Irritable bowel syndrome, GIT: Gastrointestinal tract, NDDS: Novel drug delivery systems, CRC: Colorectal cancer

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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