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Delivery of Potential Drugs to The Colon: Challenges and Strategies

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ABSTRACT

Colon-targeted drug delivery systems have been exploited to treat local diseases in the colon, systemic delivery of protein and peptide, and chronotherapeutic drugs. However, the upper gastrointestinal tract restricts the effective delivery. Therefore, several strategies are needed for drugs targeted directly to the colon, such as pH-sensitive and enzyme-sensitive polymers, bacterially degradable polysaccharides, time-dependent polymers, as well as particulate systems. Variable physiological conditions of the gastrointestinal tract in individuals cause the combinations of these strategies to ensure colonic delivery of drugs. This review presents and discusses several potential drugs and the approaches used to design and develop colon-targeted drug delivery systems for medications with particular characteristics.

Keywords: active compound, challenges, colon, colon-targeted drug delivery systems, strategies

INTRODUCTION

Colon-targeted drug delivery (CTDD) has been the focus of various investigations in recent years due to its advantages. The colon is a potential drug target because its mucosa can facilitate absorption (Amidon *et al.*, 2015). Moreover, lesser proteolytic activity and longer residence time make the colon an ideal organ to deliver drugs (Agüero *et al.*, 2017; Date *et al.*, 2016).

CTDD has been exploited for treating local diseases related to the colon, such as Crohn's disease, ulcerative colitis, irritable bowel syndrome, colon cancer, and infection (Ma *et al.*, 2019; Sardo *et al.*, 2019). This delivery method is also utilized as systemic delivery for degraded and poorly absorbed drugs in upper gastrointestinal (GI) tracts, such as protein and peptides. Delayed release in the colon after oral administration is also helpful for chronotherapy in the management of diseases. For instance, gastroesophageal reflux disease (GERD), myocardial infarction, asthma, arthritis, and stroke, which follow a circadian rhythm have a high risk with increasing symptoms at midnight (Shahiwala, 2020).

Oral colon-targeted drug delivery is expected to protect drugs from being released in the upper GI tract (Philip & Philip, 2010). However, the location of the colon in the distal end of the GI tract is an obstacle. Drugs administrated orally pass through the GI tract with a pH ranging from a strong acid medium in the stomach between 1.3 – 3.5 to almost neutral in the small intestine namely 7 – 7.4, and weak acid in the colon at 6 – 8. Hence, most of the drugs might be unstable or inactive due to the acidic environment (Lu *et al.*, 2016). The GI tract also contains several pancreatic enzymes, bicarbonates, bile salt from the bile duct, and enzymes located in colon microorganisms. They cause a reduction of effectiveness in drugs that are susceptible to these chemicals (Cook *et al.*, 2012). Several strategies are needed to delay drug release until it reaches the colon to overcome these obstacles. Therefore, this review presents several techniques used for the delivery of drugs with particular characteristics to the colon.

COLON AS A POTENTIAL AREA FOR DRUG ADMINISTRATION

The colon is considered to be a prospective absorption area for drugs that must not be released in the stomach or small intestine due to irritation or degradation in a medium with low pH and high intensity of digestive enzymes (Akala *et al.*, 2003). Colonic mucosa facilitates absorption thereby making the colon an ideal organ for drug delivery (Amidon *et al.*, 2015). The colon is also potentially

used for drug delivery because it has a less hazardous environment compared to the stomach along with a longer residence time, and better response to absorption enhancers (Agüero *et al.*, 2017). Additionally, low proteolytic activity, decreased CYP3A4 activity, and reduced P-gP expression are also advantages of CTDD (Date *et al.*, 2016).

Given that the pH of the colon is close to neutral, its environmental condition is more favorable for most drugs (Gupta *et al.*, 2001). There is a pH difference along the digestive tract as indicated (Figure 1). The gastric environment is strongly acidic with a pH of 1.5 – 2 in the fasted state. It rapidly rises along the small intestine to 6 and 7.4 in the duodenum and the terminal ileum, respectively. However in the cecum, the pH decreases to 6 and increases to 6.7 in the colon (Hua, 2020). The location of the colon at the distal end causes the need for strategies in CTDD systems to protect drugs from being released in the upper gastrointestinal tract.

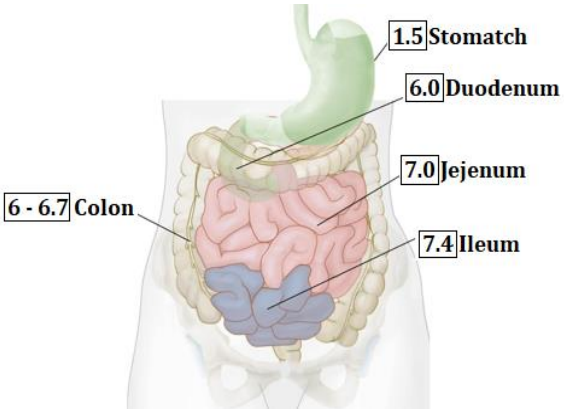

Figure 1. The differences in pH along the GI tract.

The population of microbes that colonize the large intestine is significantly higher than those in the small intestine and these microbes can catalyze various enzymatic reactions (Patel *et al.*, 2011). Therefore, natural and synthetic polymers can be used as drug carriers for prodrugs or in colon targeting due to their resistance to degradation by local bacterial species combined with the ability to resist digestion in the small intestine. It has been widely used as a matrix-forming agent or coating in CTDD (Maroni *et al.*, 2013).

Anaerobic bacterial metabolism in the colon leads to the local accumulation of short-chain fatty acids, which lowers the pH of the cecum and ascending colon (Nugent, *et al.*, 2001). Meanwhile, along the transverse and descending colon, a neutral to weakly alkaline pH environment is regained due to the absorption of fermentation products. This difference has been exploited to obtain colon-targeted drug delivery, using polymers with enteric solubility or pH sensitive coating agents (Maroni *et al.*, 2013). The use of these coatings is intended to prevent the release of drugs in the upper gastrointestinal tract because these agents are insoluble in gastric pH, but begin to dissolve and release drugs at the terminal ileum (Sardo *et al.*, 2019).

Compared to the small intestine, a stronger hydrostatic pressure can be generated in the lumen of the colon due to the intense contraction of smooth muscle and the higher viscosity of the colon contents (Takaya, *et al.*, 1995). Therefore, a relatively brittle hydrophobic film, which is capable of mechanically resisting stress conditions occurring in the proximal intestine has been investigated as an approach to obtain drug absorption in the colon (Maroni *et al.*, 2013).

The standard transit time along the small intestine is three hours due to the different dosage form characteristics as well as the feeding status of the subject, while solid substrates will remain in the colon generally for a longer period regardless of the limited organ length (Davis, 1985). This indicates that slow development of colon contents can reduce the frequency of propulsive peristaltic waves (Wilson, 2010). Therefore, formulations designed for the timely initiation of drug release through the coating layer were used to target the colon after the lag phase has been programmed to cover the entire transit time of the small intestine (Maroni *et al.*, 2010). This system requires an enteric coating due to the residence time of the drug in the stomach. Gastric emptying time is highly dependent on various physiological and pharmaceutical variables, hence, the residence time in the stomach is unpredictable (Maroni *et al.*, 2013).

In general, the colon is more suitable for the mucoadhesive drug delivery system than the stomach and small intestine due to its thicker mucus layer and less motility (Gamboa & Leong, 2013). This ability is useful for inflammation management in the epithelium of the colon, such as colon cancer with mucoadhesion properties. Prolonged mucosal contact potentially increases the uptake of drug flux along the mucosa of the colon (Boddupalli *et al.*, 2010).

Table I. Specific characteristics of various active compounds that are potentially delivered to the colon

Characteristics	Drugs
Drugs for local treatment in the colon; undergo rapid and extensive absorption in the upper GI tract	Mesalazine, capecitabine, resveratrol, and curcumin
Drugs degraded in the stomach and small intestine	Insulin, curcumin, and calcitonin
Drugs metabolized in the upper GI tract	5-Fluorouracil and resveratrol
Drugs that undergo extensive first-pass metabolism	Budesonide, nicotine, curcumin, resveratrol, and propranolol
Drugs with systemic side effects	Cyclosporine, capecitabine, and celecoxib
Drugs with local side effects in the GI tract	Indomethacin
Drugs that interact with P-gP	Propranolol
Drugs requiring delayed release	Theophylline, propranolol, and indomethacin
Drugs used to produce local effects on colon	Tetrandine and celecoxib
Drugs that are utilized colonic mucosa to induce antibody production	Recombinant Hepatitis B surface Antigen (HBsAg)

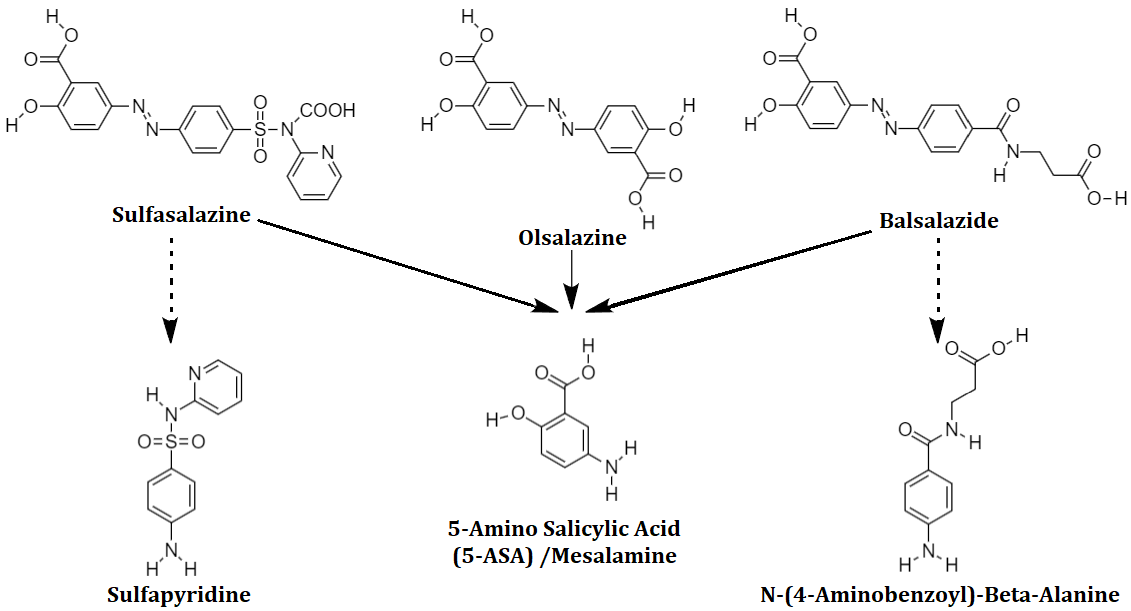

Figure 2. 5-ASA formation from sulfalazine, balsalazide, and olsalazine by azoreductase

Additionally, the interaction of positively charged nanoparticles with negatively charged mucin residues allows small particles to be more efficiently absorbed through the intestinal epithelium at physiological pH (Salvioni *et al.*, 2016).

DRUG CANDIDATES FOR COLON DELIVERY

The selection of a drug to be delivered to the colon is considered based on the specific characteristics and/or purpose possessed by the active compound. The summary of the features for various active compounds that are potentially delivered to the colon (Table I).

STRATEGIES USED FOR DELIVERY OF EACH DRUG TO THE COLON

Colon Diseases Therapeutic

This review focuses on drugs for local treatment in the colon such as Inflammatory bowel disease, colon cancer, intestinal fibrosis, and others. The CTDD strategies used for colon disease therapeutic are depicted (Table II).

Table II. Strategies used in Colon Targeted Drug Delivery for Colon Diseases Therapeutic

Disease	Drug	Carier	Excipient	Study	Result	Reference
Inflammatory Bowel Disease (IBD)	Mesalazin	Prodrug	Chondroitin Sulfate	*In vitro*	The system is selective in the intestinal environment and has mucoadhesive ability	(Cesar *et al*., 2018)
			Chitosan (amide bonding)	*In vitro*	5-ASA is not relesed in GI simulated fluids	(Zou *et al.*, 2005)
			Chitosan (azo via 4-aminobenzoyl spacer bonding)	*In vitro*	Sustained release of 5-ASA for 24 hours, but lower efficient than sulfasalazine	(Nalinbenjapun & Ovatlarnporn, 2019)
		Polysaccharides based macroparticle	Eudragit	*In vitro*	Complete drug release in the colon; drug release in the stomach can be limited	(Sharma *et al.*, 2019)
		Alginate Microsfer	Eudragit FS 30D	*In vitro*	High degree of protection against premature drug release in the stomach and small intestine, colonic drug release ~90%	(Patole & Pandit, 2018)
		Human serum albumin nanoparticle	Eudragit FS 30D	*In vitro*, *In vivo* (mice)	Significant decrease in disease activity index value & ratio Colon weight/length	(Iwao *et al.*, 2018)
	Nicotine	Nicotine-Carbopol 974 P Capsule	Eudragit L	*In vitro*	Drug release is delayed until it reaches the ileum; drug released continuous for 6 hours; have mucoadhesive properties	(Green *et al.*, 1999)
		Nicotine-pectinate Tablet	Eudragit E and Calcium Pectinate	*In vitro*	The formulation passes through the stomach and the drug is released 2-3 hours after passing through the stomach (lag time).	(Penhasi *et al*., 2020)
	Cyclosporine A	Nanoparticles	PLGA	*In vitro*, *In vivo*	The system is capable of targeting the drug to the inflamed mucosa & improving colitis parameters; produce controlled local release	(Melero *et al*., 2017)
		PLGA Nanoparticles	Eudragit FS 30D	*In vitro*	The system is able to avoid burst release and showed sustained release in the inflamed colon	(Naeem *et al*., 2018).
		Lipid Nanoparticles	Eudragit FS 30D	*In vitro*	The formulation is not able to reduce	(Guada *et*

					inflammation in the colon	*al.*, 2016)
	Budesonide	Prodrug	Dextran	*In vitro*	The conjugate is stable on the release medium for 6 hours; release 2x increase in colon simulated fluid	(Varshosaz *et al.*, 2009)
		Microparticles	PLGA and Eudragit S100	*In vivo* (rat)	Controlled specific release in the terminal ileum and proximal colon; release is inhibited at acidic pH	(Krishnamachari *et al.*, 2007)
		M-bud (Silica Microparticle coated by selective azo-molecular gate)	PLGA and Eudragit S100	*In vivo* (rat)	M-buds are effectively released in the colon; healing results are the same as commercial drugs (Entocord®)	(Ferri *et al.*, 2019)
		Nanoparticles	Eudragit FS 30D & Eudragit RS100	*In vitro*, in vio (mice)	Colon specific drug release and distribution; nanoparticles able to relieve colitis	(Naeem, Choi, *et al.*, 2015)
		Nanoparticles	Azo poliuretan and Eudragit S100	*In vitro*, *In vivo*	Accumulates selectively in the inflamed colon; clinical activity scores, colon/body weight ratio, myeloperoxidase activity, and proinflammatory cytokine levels decreased	(Naeem, Choi, *et al.*, 2015)
		Microcrystallin celulose pelet dispersed in syrup	Eudragit S100, RSPO, RL100, E100	*In vitro*	The release of sustained release in the colon	(Ronchi *et al.*, 2019)
Colon Cancer	5-Fluorourasil	Liposome conjugated folic acid	Folic acid	MTT; *In vivo*	Liposomes have cytotoxic activity; significant decrease in volume tumor	(Handali *et al.*, 2018)
		Nanoparticle PLGA	PLGA		The anticancer activity of 5-FU was increased; the exposure time required to achieve a therapeutic effect is reduced	(Tawfik, Ahamed, Almalik, *et al.*, 2003)
		Chitosan Nanoparticles	Eudragit S100	*In vitro*	The formulation protects the drug from being released in the gastric environment & increases drug localization in the colon area with sustained release for 24 hours	(Tummala *et al.*, 2015)
		pH/enzim responsive Hydrogel	Olsalazin-AC co-hydroxyetyl metacyrlat and metacrylic acid	*In vitro*	5-FU is released locally in the colon & can induce cancer cell necroptosis	(Ma et al., 2019)
	Capesitabine	Beads	Chitosan Succinate and Alginate	*In vitro*	High degree of protection from premature drug release in simulated	(Sinha et al., 2018)

					upper GI tract conditions; drugs can be delivered to the colon	
		Pellet	Surelease® (polimer sustained release) and Eudragit S100/L100	*In vitro*	The formula is able to withstand the release of drugs in the GI tract & shows sustained release for 24 hours	(Pandey *et al*., 2018)
		Nanoparticles PLGA – modified with chitosan	Eudragit S100	*In vitro*	Mucoadhesion properties are formed; in simulated colonic medium burst release followed by sustained release	(Rajasree *et al*., 2018)
	Resveratrol	Calcium pectinate Beads combined with polietilenimin (PEI)	polietilenimin (PEI)	*In vitro*	The formulation can prevent drug release in simulated conditions of the upper GI tract	(Das & Ng, 2010)
		Chitosan-Zinc-Pectinate-PEG Nanoparticles	Chitosan-Zinc-Pectinate-PEG	*In vitro*	Nanoparticles are able to protect resveratrol from being released in simulated conditions of upper GIT-to-colon transit.	(Andishmand *et al.*, 2017)
		Nanoparticles	Gellan gum and Pectin	*In vitro*, *In vivo* (rat)	Drugs may be protected against degradation in the upper GI tract; has low permeability and high retention in rat intestinal tissue	(Prezotti *et al*., 2020)
	Curcumin	Modified pectin and chitosan conjugated nanoparticles	Modified pectin and chitosan	*In vitro*	NPs aggregate upon exposure to mucin at simulated colonic pH resulting in mucoadhesive properties	(Sabra *et al*., 2019)
		Nanoparticles	PF127	*In vitro*	Strong anti-inflammatory capacity	(Zhou *et al.*, 2019)
		Spora Bacillus conjugated with folic	Folic acid	*In vitro*, *in vivo*	Drug released in the colonic area; The bioavailability of oral curcumin is increased, the retention time is extended, has a strong colonic anticancer effect	(Yin *et al.*, 2018)
		Liquisolid tablet	Eudragit and Guar Gum	*In vitro*	Dissolution of curcumin increases, drug release in the stomach and small intestine is limited	(Kumar *et al*., 2018)
Intestinal Fibriosis	Tetrandrine	Beads	Alginate/PVA; alginate/CMC	*In vitro*	Premature drug release in HCl medium pH 1.2	(Iswandana, Amangkoe, & Isnaini, 2018)

			Calsium alginate/HPMC; alginate/Chitosan	*In vitro*	High drug release in HCl medium pH 1.2	(Iswandana, Mutia, & Widyaningrum, 2018)
		Calcium pectinate Beads	Eudragit L100	*In vitro*, *in vivo* (rat)	Beads are found in the intestines of rats and have a tolerance to pH upper GI tract	(Iswandana, Putri, Sandiata, *et al*., 2017b)
		Chitosan-TPP Beads	Cellulose acetate phtalate (CAP)	*In vitro*, *in vivo*	Optimal protection against gastric acid and able to deliver tetrandrin to the intestine	(Iswandana, Putri, Dwiputra, *et al*., 2017a)
		Calcium alginate beads	Cellulose acetate phtalate (CAP)	*In vitro*, *in vivo*	Capable of resisting the release of tetrandrine in the gastric environment and producing release in the colon	(Iswandana, Putri, *et al.*, 2018)
		Lipid nanocapsule (tetrandrine-phospholipid)	Phospholipid	*In vitro*, *in vivo* (rat)	Rapid release in the first hour at pH 6.8, followed by a 12-hour sustained release; Significantly increased bioavailability compared to tablets	(Zhao *et al.*, 2013)
		Self-Nanoemulsifying Drug Delivery System (SNEDDS)		*In vitro*, *in vivo* (rat)	The dissolution rate at pH 1.2 and pH 6.8 was much faster than tablets; Bioavailability increased 2.33 times compared to tablets	(Liu *et al*., 2018)
Other	Celecoxib	Nanomixed micelles (pulsatile)	Carbopol	*In vitro*, *in vivo* (rabbit)	A target release profile was achieved with 88.35% of the dose released after an 8-hour lag period; showed a protective effect against experimentally-induced colitis	(El-hady *et al*., 2020)
		Microparticles	Eudragit	*In vitro*, *in vivo* (rat)	No release in acidic medium, release starts at pH 7.4; colonic inflammation and damage	(Bazan *et al*., 2016)
		Tablet	Guar gum	*In vitro*, *in vivo* (human)	The tablet only releases 4% of the drug in the physiological environment of the stomach and small intestine, in the colonic fluid containing the caecal content of rat guar gum is completely degraded; Delayed Tmax, long absorption time (ta),	(Krishnaiah, Satyanarayana, Kumar, & Karthikeyan, 2002)

				decreased Cmax and absorption rate constant, decreased AUC, and increased t1/2	
	Polymer conjugate	Dextran	*In vitro*	The conjugate is protected from hydrolysis in an acidic medium, and shows rapid degradation at colonic pH and caecal-containing media.	(Shrivastava & Shrivastava, 2010)

Inflammatory bowel disease (IBD)

Inflammatory bowel disease (IBD) is a chronic condition of the colon, including Crohn's disease (CD) and ulcerative colitis (UC). The main goals in the treatment are to prevent the recurrence of inflammation and maintain remission. Nonenzymatic therapies used in the treatment of this disease include aminosalicylates, corticosteroids, immunosuppressive agents, and biologic agents.

Mesalazine (5-aminosalicylic acid (5-ASA))

5-ASA is one of the drugs of options for treating mild to moderate ulcerative colitis due to its anti-inflammatory effect. Oral administration in conventional dosage form shows rapid and widespread absorption in the upper gastrointestinal tract. The absorption can cause certain systemic side effects and low drug concentrations in the colonic area thereby decreasing the efficacy of the treatment (Sardo *et al.*, 2019).

The first commercially available 5-ASA delivery system to the colon through the oral route was carried out using the prodrug strategy with sulfasalazine, olsalazine, and balsalazide (Quetglas *et al.*, 2015). These prodrugs have been synthesized to utilize the high density of bacteria in the colon to deliver the drug to that area of the intestine. Azo bonds are used to bind the 5-ASA moiety to the carrier molecule. Due to the high molecular weight, hydrophilicity, and inadequate absorption properties in the presence of an excretory transporter, the prodrug is not absorbed from the upper GIT. Furthermore, 5-ASA is metabolized by colonic bacteria enzymes such as azoreductase (Figure II) (Sousa *et al.*, 2014).

Apart from these products, various polysaccharides have been widely used to design the prodrug of 5-ASA. Cesar *et al.* (2018) designed CTDD of 5-ASA using linked chondroitin sulfate to produce a polymeric prodrug. The *in-vitro* release study showed that the CS-5-ASA polymer prodrug conjugate was more stable in the acid environment and the system was selective in the intestines, as evidenced by higher drug release in alkaline and neutral medium than acidic medium. Moreover, the biodistribution results showed that the conjugate reached the lower GIT 6 hours after dosing and stayed for up to 8 hours without absorption in the upper part. This result strongly suggests a potential mucoadhesive profile which can prevent the 5-ASA absorption in the upper GI tract, indicating the need for dose reduction to achieve therapeutic dose (Cesar *et al.*, 2018).

The limitations of the prodrug system include drug-insufficient cleavage of chemical bonds due to diarrhea, uneven distribution of required enzymes, susceptibility of colonic bacteria to occasionally administered antibiotics, and restriction in clinical use due to certain toxicity and safety assessment issues (Ye & Langenberg, 2015). The use of pH-sensitive polymers including Asacol, Claversal, and Salofalk, coated with Eudragit was further developed to overcome these limitations. Soluble coatings are used at a specific pH based on the physiology of the gastrointestinal tract. The lag time of Eudragit increased as pH increased, but the drug release rate was slower in the condition above 5, while the solubility increases below 6.5. When Eudragit is at neutral pH in the small intestine, it is not dissolved to protect the drug, but in the colon, the presence of organic acids or fermentation by bacteria creates an acidic environment which further will dissolve the coating and release the drug (Kathiravan, 2015).

However, the varying colonic pH of each individual is a significant concern for this strategy (Sardo *et al.*, 2019). Pentasa, which is a time-dependent coating was further developed for 5-ASA delivery to the colon (Nielsen & Munck, 2007). In general, a time-dependent approach allows the use of carriers or polymers that delay drug release until the delivery system reaches the colon. Pentasa consists of mesalazine microspheres encapsulated in a semipermeable ethylcellulose membrane. This structure allows time- and water-dependent drug release, regardless of the luminal pH. Goyanes *et al.* (2015) showed that Pentasa preparations quickly degranulate in an acidic environment. The mechanism of action is by diffusion through insoluble polymers, allowing more than 50% release of the drug in an acidic environment throughout the small intestine and colon. The premature release of 5-ASA in the upper GIT can decrease the dose of CTDD (Goyanes *et al.*, 2015).

Due to discontinuity in the GI environment regarding pH, transit time, secretion, or inter and intrasubject pathologic variations, the use of only one approach will be complicated. Therefore, using the combination of drug delivery strategies to the colon might be the way to overcome these challenges. Sharma *et al.* (2019) investigated the use of combination strategies by preparing polysaccharide-based macroparticles coated with Eudragit and then compressed into tablet form. The results of the in-vitro study confirmed the cleavage of gum arabic in the presence of colonic bacteria and allowed complete drug release from this

delivery system. Furthermore, gamma scintigraphy studies also confirmed that the formed tablets might limit the release of the drug in the stomach and allow complete release in the colon (Sharma *et al.*, 2019).

Recently, nanoparticulate delivery systems have been developed to target drugs for inflammation areas. One of the main barriers to the system is the early leakage of the drug due to its large surface area, which can lead to reduced efficacy. Meanwhile, one strategy that can be used is to bind 5-ASA to nanocarriers with biodegradable covalent bonds. The products of chemical bonds are biodegradable, hence, the system might delay the release of the drug. In a study conducted by Iwao *et al.* (2018), 9 5-ASA molecules were conjugated with a molecule of Human Serum Albumin nanoparticle (5-ASA-HSA NP). Significant reductions in disease activity index and colon weight/length ratio values in the model of UC mice after 5-ASA-HSA NP administration indicate that the therapeutic effects of these nanoparticles were confirmed in-vivo. The microscopic images obtained from colonic tissue sections also show specific interactions between nanoparticles and myeloperoxidase (MPO) indicating that this formulation can potentially deliver 5-ASA to the inflamed colonic area (Iwao *et al.*, 2018).

Nicotine

Nicotine which is the active substance in cigarettes has a therapeutic role in the treatment of ulcerative colitis patients (Lakhan & Kirchgessner, 2011). One system that has been developed for nicotine delivery is the use of transdermal patches. However, several studies showed that transdermal nicotine administration is not better than the placebo in maintaining remission from ulcerative colitis (Lunney & Leong, 2012). Another study also showed that side effects occurred in two-thirds of patients, especially those who had never smoked (Green *et al.*, 1999). This indicates that CTDD through the oral route can be a promising approach. However, pharmacokinetic studies showed that most of the active nicotine is converted to cotinine through first-pass metabolism in the liver, while those that reach serum can cause side effects (Penhasi *et al.*, 2020).

Recently, a novel strategy for colonic-targeted nicotine release was developed by Penhasi *et al.* (2020) by reacting nicotine and polysaccharides, in the form of pectin, to produce a water-soluble nicotine-pectin salt called nicotine pectinate (NiP). The results showed that nicotine reaction with pectin is an effective technique to solve the problem of preparation and handling of nicotine-containing formulations as well as to produce a matrix applicable for a modified release system. The nicotine pectinate formed is then incorporated into core formulations (tablets) and subsequently coated with a film coating, a combination of calcium pectinate and Eudragit E. The results of such formulations successfully pass through the stomach in an intact form and nicotine is released only after a lag time, namely 2- 3 hours, which is equivalent to the time required for transit in the small intestine *(*Penhasi et al., 2020).

Cyclosporine A (CSA)

CSA is an immunosuppressive drug for UC therapy due to the rapid onset in patients with severe and steroid resistance (Naeem *et al.*, 2018). The delivery of cyclosporine through the oral route has obstacles that limit the bioavailability of CSA due to solubility problems. Therefore, Sandimmune Neoral®, a soft-gel-based stable microemulsion formulation which increases solubility and absorption in the upper intestine was developed. Systemic CSA therapy is limited in clinical practice because it requires monitoring drug plasma levels during treatment to prevent serious side effects such as nephrotoxicity, hypertension, seizures, renal dysfunction, opportunistic infections, and toxicity (Eun & Han, 2015). Hence, the colon-targeted drug delivery system is needed to overcome these limitations.

The use of polymeric nanoparticles needs to be considered based on their ability to accumulate in the ulcerated area of the colon over a long time. One of their uses in delivering CSA to the colon was examined by Melero *et al.* (2017) using PLGA as the polymer. The results showed that the nanoparticles formed can target drugs at inflamed mucosal areas, increase colitis parameters compared to microparticles, and produce controlled-release locally at the disease site (Melero *et al.*, 2017). However, delivery of PLGA nanoparticles has limitations such as initial burst release in the upper gastrointestinal tract and lack of pH sensitivity, making this system less efficient for specific delivery in the colon (Ali *et al.*, 2014). A single pH-dependent nanoparticle system is not recommended for the treatment of ulcerative colitis due to the rapid and complete release of the drug at pH of the ileum (Naeem, Cao, *et al.*, 2015).

Based on the results of these studies, Naeem *et al.* (2018) further developed a CSA delivery system to the colon with a combination of PLGA and Eudragit® FS30 D as copolymer sustained-release

and pH-responsive polymer respectively. The results indicated that nanoparticles can avoid sudden release in the stomach, slowly and incompletely released at ileal and colon pH, followed by delayed discharge and accurate CSA to the inflamed colon (Naeem *et al.*, 2018).

Budesonide

Budesonide is a second-generation corticosteroid, its topical potency is 200 times higher than hydrocortisone due to the higher affinity for the receptor and more significant anti-inflammatory effect (Pithadia & Jain, 2011). The drug has limited systemic bioavailability caused by extensive hepatic first-pass metabolism by the CYP3A enzyme, hence, a targeted drug delivery system was developed to overcome these limitations (Tromm *et al.*, 2011). The pH-dependent systems are one of the commercially available CTDD strategies, including Budenofalk® and Entocort®. However, these budesonide are released in the ileum and the proximal part of the colon. This single system can not be ideal for the treatment of UC with inflammation in the distal part of the colon and rectum (Sandborn *et al.*, 2012).

The use of nanoparticles as drug carriers was also developed to deliver budesonide to the colon. Naeem, Choi, *et al.* (2015) utilized a combination of a pH and time-dependent polymer which is subsequently incorporated in the budesonide-containing nanoparticles. The *in-vitro* and *in-vivo* results suggest that these nanoparticles show increased release and distribution of specific drugs to the colon compared to those with only time or pH-dependent polymers. Furthermore, the Disease Activity Index results, changes in body weight, colon length, as well as the histological and immunohistochemical properties of the colon tissue showed that nanoparticles with a combination of pH and time-dependent polymers were able to alleviate colitis induced by DSS in mice more effectively than those with pH-dependent polymers (Naeem, *et al.,* 2015).

Colon cancer

Colon cancer is one of the most common diseases and the leading cause of morbidity and mortality worldwide. Various cytotoxic drugs are used for the treatment, including 5-fluorouracil, capesitabin, resveratrol, curcumin, and others (Z. G. Ma *et al.*, 2016).

5-Fluorouracil

5-Fluorouracil (5-FU) is commonly used for the treatment of colon cancer and the metabolic rate is very high in the body. To achieve therapeutic drug levels, it is necessary to administer high doses of the drug regularly and continuously, hence, administration through the oral route is preferred over the parenteral. However, the efficacy of 5-FU is severely hampered because the dihydropyrimidine dehydrogenase enzyme can metabolize the drug in the intestinal wall immediately after oral administration (Handali *et al.*, 2018).

The 5-FU targeted delivery to the colon was carried out by Handali *et al.* (2018) using liposomes conjugated with folic acid. Meanwhile, folic acid conjugated liposomes containing 5-FU can potentially increase the therapeutic efficacy of drugs and decrease toxic side effects. It was based on the results of the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) study, which showed that the 5-FU folate-liposomes had higher cytotoxic activity in cancer cells than only 5-FU and 5-FU liposomes. Besides, the results of the *in-vivo* study showed a significant decrease in tumor volume by targeted liposomes compared to free drugs (Handali *et al.*, 2018).

Apart from liposomes, delivery can also be carried out using chitosan nanoparticles coated with Eudragit S100. An i*n-vitro* study showed that this formulation can protect drug release in the acid medium, increase drug localization in the colonic area, and achieve a sustained release for 24 hours (Tummala *et al.*, 2015).

The delivery of 5-FU to the colon using pH-responsive hydrogels or enzymes has also been widely studied, considering the variation in pH and colonic microflora in the GI tract. Ma *et al.* (2019) used olsalazine as the azo structural unit of the hydrogel. An olsalazine derivative modified by acryloyl chloride was synthesized as a cross-linking agent, then copolymerized with methacrylic acid and hydroxyethyl methacrylate to produce a hydrogel with multiple pH and enzyme responses. The results of this design indicate that 5-FU is released locally in the colon, and high local concentrations can induce necroptosis of colon cancer cells and avoid drug resistance (Ma *et al.* 2019).

Capecitabine

Capecitabine is a drug that is widely used in the treatment of colon cancer but has a short plasma half-life of 0.85 hours, thereby causing rapid elimination from the body, hence, repeated administration is needed (Arnold *et al.*, 2017). Also, the high doses required for twice-daily administration cause toxicities, such as cardiotoxicity, bone-marrow depression, diarrhea,

vomiting, nausea, and dermatitis (Sinha *et al.*, 2018). To overcome these deficiencies, CTDD through the oral route can be used to minimize the side effects of the drug while increasing the efficacy of the therapy. However, capecitabine administered orally at a dose of 1,250 mg/m^2 can be absorbed quickly and extensively in the gastrointestinal tract indicating that various strategies are needed for the drug delivery (Jena *et al.*, 2017).

Sinha *et al.* (2018) conducted a study on the efficacy of a multiparticulate system of biopolymer complex beads from alginate and chitosan succinate for the delivery of capecitabine to the colon. The results showed that the beads can protect the system from premature drug release in the simulated upper GI tract medium. This was evidenced by the swelling index, which indicated that the beads reached a maximum good swelling at a pH of 7.4 and no or little swelling at acidic pH. These beads also delivered most of the drug load to the colon, an environment rich in bacterial enzymes that degrade succinate chitosan, and produce drug release in the desired area (Sinha *et al.,* 2018).

Furthermore, Rajasree *et al.* (2018) developed the use of PLGA nanoparticles for capecitabine delivery to the colon. The NP surface was modified using chitosan and encapsulated with Eudragit S100. The *in-vitro* mucoadhesion study proved that the mucoadhesion properties of the nanoparticles formed were higher and longer than the unmodified. A rapid discharge was followed by sustained release of capecitabine in colonic simulation medium assisted by matrix diffusion (Rajasree *et al.*, 2018).

Resveratrol

Resveratrol is a phenolic compound that has therapeutic efficacy against lower gastrointestinal tract diseases, such as colon cancer and colitis (Martín *et al.*, 2006; Schneider *et al.*, 2001). The low bioavailability and very short plasma half-life are problems related to its systemic action (Das & Ng, 2010). Besides, rapid absorption in the upper GI tract and the potential for metabolism in the upper GI tract as well as the liver after oral administration limit the amount reaching the colon to produce a therapeutic effect (Das *et al.*, 2008).

Das & Ng (2010) developed a multiparticulate CTDD system by formulating resveratrol in calcium-pectinate beads. Given that the calcium-pectinate beads are unable to withstand the conditions in the acid environment and the burst release of resveratrol in the upper GI tract, polyethyleneimine (PEI) is added to the crosslinking solution to harden the beads. The addition of PEI led to the hardening of the surface along with the beads formation. The formed beads can encapsulate large amounts of resveratrol and prevent the release in the upper GI tract simulation conditions (Das & Ng, 2010).

Prezotti *et al.* further developed mucoadhesive polymer nanoparticles using a mixture of gellan gum and pectin with ionotropic nebulization and gelation techniques for resveratrol delivery to the colon. The nanoparticles formed triggered an effective modulation of the drug release rate as only 3% resveratrol was released in an acidic medium for two hours. At a pH of 6.8, the drug was released continuously, reaching 85% in 30 hours. These results indicate that polymeric nanoparticles can protect resveratrol from degradation in the upper GI tract. A study also showed that resveratrol had low permeability and high retention in the intestinal tissue of mice. This is advantageous for effective CTDD due to the accumulation of the drug in the colon, thereby increasing local action, and interfering with systemic absorption (Prezotti *et al.*, 2020).

Curcumin

Epidemiological studies showed that curcumin, which is a natural polyphenol compound, can potentially reduce the risk of various types of cancer (Kumar *et al.*, 2018). It also has potent antioxidant and anti-inflammatory activities (Park *et al.*, 2013). However, low solubility, rapid clearance from the systemic circulation, degradation of gastric and intestinal enzymes, high intestinal absorption, high hydrophobicity properties, as well as hepatic metabolism can decrease curcumin bioavailability and hinder its application as an effective chemotherapeutic agent in the treatment of colorectal cancer (Frank *et al.*, 2014).

Various studies have been conducted to deliver curcumin directly to the colon. One of the strategies that were successfully developed is through a nanoparticle delivery system conjugated with modified pectin and chitosan. Nanoparticles formed spontaneously aggregate when exposed to mucin at simulated colonic pH and produce mucoadhesive properties that can prolong the contact time between curcumin and cancer cells thereby increasing treatment efficacy (Sabra *et al.*, 2019).

Furthermore, Yin *et al.* (2018) developed biological carriers to overcome the shortcomings of synthetic polymers and lipid particles. The

biological particles used as carriers were Bacillus spores whose outer layer and folate are covalently bound to curcumin (SPORE-CUR-FA). The results showed that the carrier can release the drug in the intestinal tract, primarily in the colonic region by taking advantage of its tolerance to harsh conditions. The released drug can transit the gastric barrier and the outer layer of spores after sprouting in the colon. Pharmacokinetic studies confirmed that this system can significantly increase the curcumin bioavailability by oral administration and prolong the retention time *in vivo*. Also, *in vitro* and *in vivo* studies reported that these curcumin-containing carriers have a strong colonic anticancer effect (Yin *et al.*, 2018).

Intestinal fibrosis

Intestinal fibrosis is a colonic disease caused by excessive deposition of the extracellular matrix which causes impaired wound healing in the intestine and chronic inflammation (Iswandana *et al.*, 2016).

Tetrandrine

Tetrandrine is an alkaloid that acts as an inhibitor in the transforming growth factor (TGF) signaling pathway (Westra *et al.*, 2014). It is potentially used in the treatment of intestinal fibrosis. The treatment of inflammation will be effective when the drug is released in the affected area. Hence, a delivery system is needed for tetrandrine to reach the colon (Iswandana *et al.*, 2017a, Iswandana *et al.*, 2017b). The use of beads as carriers can be a strategy in CTDD systems because of the ability to control drug release.

Iswandana *et al.* (2017b) conducted a study related to beads in the drug delivery to the colon, using a calcium pectinate beads formula containing tetrandrine coated with several pH-sensitive polymers. Among the formula, calcium pectinate beads coated with Eudragit L100 showed the lowest cumulative drug release of 3.54% and 13.58% in pH 1.2 of HCl and 7.4 of phosphate buffer, respectively. Furthermore, at pH 6.8 of phosphate buffer in the absence of enzymes, drug release is significantly increased. The i*n-vitro* results were further confirmed by the *in-vivo* study showing that the coated beads can be found in the intestines of mice and have a tolerance to the pH of the upper GI tract (Iswandana *et al.,* 2017b).

Additionally, the development of a calcium alginate-tetrandrine formulation coated with Eudragit L100-55 or L100, hydroxypropylmethylcellulose phthalate (HPMCP), cellulose acetate phthalate (CAP) was also carried out by Iswandana *et al.* (2018). The i*n-vitro* results showed that CAP - calcium alginate beads can withstand the release of tetrandrine in the gastric environment. This led to a better drug release in colonic conditions of 67.68%. Similarly, the *in-vivo* results also showed beads' ability to sustain drug release in the stomach (Iswandana *et al.*, 2018).

Other

Celecoxib

Celecoxib is a class of selective cyclooxygenase 2 (COX-2) inhibitors used for colitis treatment, prevention, and as a chemoprotective agent in adenomatous polyposis-induced colorectal cancer (Arber *et al.*, 2006; Bazan *et al.*, 2016). The COX-2 inhibitor has safety and tolerability in IBD patients but it also has cardiovascular side effects when used for a long time (Miao *et al.*, 2014). Therefore, specific and selective delivery to the colon is required to produce local effects and minimize side effects. The low solubility and dissolution rate of celecoxib in the gastrointestinal tract is a challenge in administering the drug through the oral route, hence, various strategies are needed (El-hady *et al.*, 2020).

Krishnaiah *et al.* (2002) studied CTDD with guar gum as a carrier to be degraded by colonic bacteria. A total of 4% celecoxib was released from guar gum matrix tablets in the physiological environment of the stomach and small intestine. Furthermore, the matrix formulation containing 20% guar gum was degraded entirely in the simulated colonic fluid. Subsequent *in-vivo* evaluations were carried out for these formulations in human volunteers. The results showed that the drug is not released significantly in the stomach and small intestine, but is delivered to the colon (Krishnaiah *et al.*, 2002).

Another strategy was developed by Shrivastava & Shrivastava (2010) through the preparation of colonic specific polymer conjugates for celecoxib using dextran as carrier macromolecules. Succinic acid is then used as a link between celecoxib and dextran because it does not have free groups to be conjugated. The *in-vitro* results of the conjugate showed no hydrolysis in simulated gastric fluid with pH 1.2, but rapid degradation was observed in colonic pH and medium containing caecal content (Shrivastava & Shrivastava, 2010).

Bazan *et al.* (2016) also improved the use of the particulate system by formulating selectivity in microparticles using Eudragit as a pH-dependent polymer for targeted colonic delivery. The *in-vitro* results showed no release in an acidic medium for

two hours, followed by drug release at pH 7.4 with Eudragit S100. Biochemical and histopathological examinations showed that these microparticles can reduce inflammation and damage to the colon (Bazan *et al.*, 2016).

A new strategy for targeted colonic delivery of selective enzymes developed by El-Hady *et al.* (2020) uses a pulsatile capsule system with nano mixed micelles as a selective carrier to increase solubility. The study showed that a pulsatile capsule containing 75% Carbopol as a time-dependent polymer yielded 88.35% of the dose released after a lag period of 8 hours. The system has a protective effect against experimentally-induced colitis (El-hady *et al.*, 2020).

Protein and Peptide

Recent advances in pharmaceutical biotechnology have made it possible to treat a wide range of life-threatening diseases using therapeutic proteins. The recombinant protein therapy was developed for vaccines and the treatment of several diseases, such as inflammation, cancer, and genetic disorders. Various strategies are needed to optimize delivery directly to the colon due to the large size of the protein which can limit the absorption process as well as to protect the protein from the acidic environment and proteolysis. The CTDD strategies used for protein/peptides (Table III).

Insulin

Insulin is a polypeptide hormone used to treat diabetes mellitus and is usually given by the subcutaneous route. This administration causes several disadvantages for patients, such as pain during the injection, leading to decreased patient comfort, weight gain, hypoglycemia, edema, lipodystrophy, and skin infections. Besides, the subcutaneous route is not sufficient because only 20% of insulin given can reach hepatic circulation (Macedo *et al.*, 2020).

Administration of insulin orally has obstacles related to poor bioavailability due to its hydrophilicity, large size, and enzymatic degradation (Patel & Mayur, 2013). Several strategies to overcome the problems have been utilized, including permeation enhancer, protease inhibitor, and particulate delivery system. Recently, insulin delivery through the oral route by nanoparticulate system has attracted significant attention following its submicron size and high specific surface area (Elsayed, 2012). Insulin loaded in this carrier can avoid degradation in GI, thereby increasing the absorption and bioavailability (Verma *et al.*, 2014). In recent years, nanoparticulate carrier of degradable polymers has been a promising alternative for increasing the uptake and transport of therapeutic protein given orally across the epithelial membrane without ruining its integrity (Fang *et al.*, 2019).

Salvioni *et al.* (2016) developed a formulation of polyethyleneimine nanoparticle-containing insulin which was incorporated in pellet core and then coated with three layers, including Methocel® E50 and PEG 400, Eudragit® NE 30D-Explotab® CLV, as well as gastro-resistant film Aqoat®. The formed pellet is then combined with sodium glycocholate. The formulation coated with three film layers showed gastro-resistant properties and delayed-release *in vitro*. Furthermore, the results showed a synergistic effect of insulin nano-formulation and three-layer pellet system encapsulation for colon delivery with a long-lasting hypoglycemic effect (Salvioni *et al.*, 2016).

In the study conducted by Morales-Burgos *et al.* (2019), insulin aggregates were formed using glutamic acid and then incorporated in the arabinoxylan (AX) microsphere. Arabinoxylan is potentially used for delivery as the polysaccharide is slightly affected by pH changes and fermentable by colon microbiota. The consideration of using aggregates is to overcome problems related to the small diameter of insulin, which can harm its retention in the microsphere polymer network (Morales-Burgos *et al.*, 2019). However, to increase insulin absorption and biological activity, the aggregates must separate when released. Dynamic Light Scattering measurement showed that aggregates of insulin-glutamic acid are reversible in intestine conditions with a pH of 6.8. The i*n-vitro* results indicated that the formulation formed is stable in the simulation stomach and the small intestine environment with the low release of insulin amounting to 20%. This implies that most insulin remains in the microsphere and is available for release in the colon.

Calcitonin

Calcitonin is an active peptide from 32 amino acids that can maintain calcium balance, inhibit osteoclast activity, as well as decrease serum calcium and induce absorption in bone (Li *et al.*, 2018). In general, calcitonin is used for bone disease management, such as Paget's disease, hypercalcemia, and osteoporosis. Compared to other sources, salmon calcitonin can be administered by intramuscular and subcutaneous injection, as well as nasal spray formulation (Torres-Lugo & Peppas, 2000).

Table III. Strategies used in Colon Targeted Drug Delivery for Protein/Peptide Delivery

Protein/Peptide	Carier	Excipient	Study	Result	Reference
Insulin	Enhancer (Sodium Glycocolate)	Sodium Glycocolate	*In vivo* (dog)	Increased & prolonged insulin absorption in the colon	(Katsuma *et a*l., 2006)
	Nanoparticles	Chitosan Quartener	*In vitro*	NP can facilitate insulin uptake, low burst effect, steady insulin release properties	(Bayat *et al*., 2008)
	Microsfer	Arabinoxylan	*In vitro*	Stable formulation in a simulated stomach & small intestine environment with low insulin release	(Morales-Burgos *et al.*, 2019)
	Pellet nanoparticles PEI and Enhancer (sodium glycocolate)	Methocel ® E50 & PEG 400, Eudragit ® NE 30D, Explotab ® CLV, Aqoat®	*In vitro*, *In vivo* (rat)	The insulin release is delayed and the formulation is gastroresistant; produces a significant & long-lasting hypoglycemic effect	(Salvioni *et al*., 2016)
	Mesopori phosphonate (ZrBPMP-3) pH sensitive and Enhancer (sodium glycocolate)	dipcoating lag time films	*In vitro*	Minimum release in stomach & small intestine; insulin release in the colon with dual control (time & pH)	(Ren *et al.*, 2013)
Calcitonin	Hydrogel	Dextran	*In vitro*	The rate of release increased markedly in colonic medium containing dextranase; release lasts up to 17 hours	(Basan & Orbey, 2007)
	Nanofiber (liposome coated with pectin)	Sodium alginate	*In vitro*	Calcitonin is released in a sustained and targeted colon; the release of calcitonin in the simulated gastric and intestinal fluids can be reduced	(Feng *et al.*, 2019)
HbsAg	Nanoparticles + MPLA	Eudragit	*In vitro*, *in vivo* (rat)	NPs can protect the antigen from gastric degradation and result in the release of as much as 20 -23% at pH 7-7.2 (SCF); absorption and distribution of effective nanoparticles in the colon and results in enhanced immune response	(Sahu & Pandey, 2019)
	Minicapsule (Lyophylized Nanoparticles + MPLA)	Eudragit	*In vitro*, *In vivo* (rat)	NP release assay (PBS pH 7.4): release (2–11%) in first 2–3 hours & maximum release (17.5% ± 1.45%) for 5–6 hours; minicapsule dissolution test: no NP release at pH 1.2 and 4.5, release (40–45% ± 4.2%) at pH 7–7.4; *in vivo* test: administration of minicapsules produces approximately 2-3x more mucosal immune response compared to marketed vaccines	(Sahu, Kaurav, & Pandey, 2019).

Table IV. Strategies used in Colon Targeted Drug Delivery for Chronotherapy Management Diseases

Protein/Peptide	Drug	Carier	Excipient	Study	Result	Reference
Rheumatoid Arthritis	Indomethasin	Xanthan gum	Eudragit L100/S100	*In vitro*	Very low upper GI drug release, controlled release for 14-16 hours in the colon	(Asghar *et al.*, 2009)
		Liquisolid tablet	Eudragit RL 100, guar gum, pectin, chitosan	*In vitro*	Very low release in the initial phase, followed by a slow release for 24 hours	(Elkhodairy, Elsaghir, *et al.*, 2014)
Nocturnal Asthma	Teophylline	Tablet	HPMC, Eudragit S100, Etyl cellulose	*In vitro*, *In vivo*	Tablets do not release drug in the upper GI tract, release begins at pH 6.4; the tablet remains intact until it reaches the colon & release begins after a lag time of 5 hours	(Patel & Amin, 2011)
		Coated tablet	Chitosan	*In vitro*	Minimum release at pH 1.2 and 7.4; release > 50% in alkaline medium containing rat caecal	(Yassin *et al.*, 2012)
		Microcapsule (pulsatile)	Eudragit L100/S100, CAP	*In vitro*, *in vivo*	Discharge lasts for 24 hours; system releases drug in GI tract after programmed lag time for nocturnal asthma	(Mastiholimath *et al.*, 2007)
		Guar gum microsfer	Eudragit	*In vitro*	Release protected from gastric acid environment, controlled release after colonic lag time	(Verma *et al.*, 2012)
		Chitosan Beads coated in enteric capsule	Eudragit S100	*In vitro*	The release in gastric medium and phosphate buffer pH 6.0 was not significant, the release occurred in phosphate buffer solution pH 7.2	(Reza *et al.*, 2004)
Hypertension	Propranolol	Tablet	Tamarind gum	*In vitro*	The formulation can control drug release until it reaches the colon with < 15% drug released in the first 4 hours (lag time to reach the colon), can prolong release for a long time	(Newton *et al.*, 2015)

Among these routes, nasal administration is the most preferred because it is more comfortable and easily accepted by patients than repeated injection. In addition, nasal spray formulation can irritate nasal mucosa and causes rhinitis, rhinorrhea, and allergic rhinitis (Ugwoke, *et al*., 2001). The bioavailability of salmon calcitonin through nasal spray is only approximately 3% (Li *et al.*, 2018), hence, there is a need to develop other alternatives, namely the oral route.

Salmon calcitonin delivery through the oral route is a challenge due to the instability and poor bioavailability in upper GI tracts condition (Li *et al.*, 2018). Therefore, the CTDD systems can be used to overcome these problems. One of the approaches applicable is formulating dextran hydrogel synthesized with cross-linking dextran and epichlorohydrin for delivering salmon calcitonin specifically to colon *in-vitro*. The results showed that the release rate is increased sharply by glucosidic bond degradation from dextran hydrogen in colon media containing dextranase. The release occurs for 17 hours and the total amount released reaches 84.9%. The measurement of release in the simulation stomach medium was not conducted hence, some of the drug load might be released in this medium or entrapped in dextran hydrogel (Basan & Orbey, 2007).

Feng *et al.* developed a strategy of calcitonin delivery by formulating multiple CTDD through the incorporation of liposome in nanofiber with coaxial electrospinning. In this formulation, sodium alginate can retain stomach stimulated medium and be degraded by polysaccharides in the colon. Calcitonin is encapsulated in liposome through film dispersion method and further coated with pectin to improve its stability. Furthermore, coated liposome is encapsulated in nanofiber. The *in-vitro* results showed that encapsulated calcitonin is sustained and released in the colon. Besides, this nanofiber can also reduce calcitonin release in the simulation stomach and intestine fluid. These results demonstrate the superiority of the multi-unit carrier to colon-targeted delivery (Feng *et al.*, 2019).

Recombinant Hepatitis B Surface Antigen (HBsAg)

Hepatitis B is a severe liver disease caused by the Hepatitis B virus (HBV) infection which can be effectively prevented by vaccination (Roberts *et al.*, 2005). CTDD can be used because antigen delivery on colonic mucosa stimulates the general immune system and induces strong antibody production (Sahu *et al.*, 2019). Sahu & Pandey (2019) developed HBsAg formulation in Eudragit nanoparticle-containing Monophosphoryl lipid A (MPLA) as an adjuvant. The results showed that nanoparticles formed can protect antigen from stomach degradation, while fluorescent spectroscopy, differential scanning calorimetry, and antigen integrity with SDS-PAGE indicated no change in the antigen structure during and after formulation. Moreover, the *in-vivo* study results in rats confirmed an increased immune response (Sahu & Pandey, 2019).

Sahu *et al.* (2019) also developed mucosa immunization with HBsAg loaded in the lyophilized nanoparticle with MPLA and delivered to the colon using the mini capsule coated with Eudragit. The lyophilized NP in PBS pH 7.4 showed 2-11% release at the first 2-3 hours and reached the maximum of 17.5% ± 1.45% between 5 and 6 hours. Meanwhile, the dissolution results of the mini capsule showed that there is no release in pH between 1.2 and 4.5 (SGF and SIF), while at 7 – 7.4 (SCF), 40–45% ± 4,2% of the drug were released (Sahu *et al.* (2019). This mini capsule administration produces mucosa immune response that is approximately two to three times stronger than the commercial vaccine.

Chronotherapy Management Diseases

Chronotherapeutic refers to a method of treatment in which the availability of drugs *in-vivo* is regulated according to the rhythm of the disease to optimize therapeutic results and minimize side effects. This method has been used successfully in treating diseases, such as rheumatoid arthritis, asthma, and hypertension, which have early symptoms. The CTDD strategies used for chronotherapeutic (Table IV).

Indomethacin

Indomethacin is a nonsteroidal anti-inflammation drug used for treating osteo and rheumatoid arthritis. Approximately 35 – 50% of patients given indomethacin orally experienced local side effects in the GI tract (Goodman & Gilman, 2011), but the CTDD systems can be used to reduce side effects. Elkhodairy *et al.* (2014) developed a tablet matrix formulation with the liquisolid technique. In this system, Eudragit RL100 was used as a time-dependent polymer. A combination of guar gum, pectin, and chitosan was used as a bacterial degradable polysaccharide. The results showed minor release in the early phase, followed by a sustained release for 24 hours (Elkhodairy *et al.*, 2014).

Theophylline

Theophylline can be used to treat nocturnal asthma when administered at a certain time and it has good bioavailability in the colon area. Patel *et al.* (2011) developed CTDD systems by formulating tablets with hydroxypropyl methylcellulose for controlling drug release after coating with Eudragit S100: ethylcellulose, which can delay drug release. The results showed that the tablet formed no premature release at the upper GI tract, and drug release began in colonic media, with a pH of 6.4 after a lag time of 5 hours. The *in-vivo* results in rabbits showed that the tablet remains intact before reaching the colon (Patel *et al.*, 2011).

Furthermore, Yassin *et al.* (2012) formulated a tablet coated with chitosan. The results showed minimal release after 5 hours in pH of 1.2 and 7.4, then more than 50% were released after 4 hours in a medium containing rat caecal content (Yassin *et al.*, 2012). Besides, Verma *et al.* (2012) developed a guar gum microsphere containing theophylline coated with Eudragit. The *in-vitro* results showed that theophylline is protected from the acid environment by coating with Eudragit and controlled release occurred after the lag time is achieved (Verma *et al.*, 2012).

Propranolol

Propranolol hydrochloride is used for treating several cardiovascular diseases, such as angina, tachycardia, and hypertension. A secretory transporter namely P-glycoprotein located in epithelial cells is responsible for the low bioavailability. Newton *et al.* (2015) developed the drug delivery to the colon by formulating the tablet matrix using tamarind gum. The prepared formulation can control drug release until it reaches the colon. Approximately less than 15% of the drug is released in the first four hours, which is the estimated lag time of dosage to reach the colon (Newton *et al.*, 2015).

FUTURE PERSPECTIVE

Particulate systems, including multiparticulate such as beads, pellet, and microsphere, as well as microparticles, and nanoparticles, have been used to formulate CTDD systems. These systems are based on their advantages, for example, beads can control drug release, microparticles are sustained in colitis sites with a thick layer of mucus, and nanoparticles which accumulate in the ulcerated area of the colon for a long time. Most studies combine several strategies to generate optimal colonic drug delivery because the physiological condition of the GI tract varies in each individual.

The use of nanoparticles as carriers appears to be the ideal form of delivery for most drugs. This is because they are stable in the GI environment and can protect the encapsulated drug from extreme pH as well as enzyme degradation. Furthermore, surface modification of nanoparticles with different physicochemical properties allows them to penetrate the mucus barrier and target the drug to a specific area obtained by attaching the targeting ligand to the particle surface. These nano-sized carriers can also accumulate drugs in the colon inflamed by the epithelial enhanced permeability and retention (eEPR) effect thereby increasing the residence time in the target area and efficacy. Drugs loaded in nano-formulations enter cells through the endocytosis process, hence, the interactions with P-gP can be avoided (Lu *et al.*, 2016). Nanoparticles can control and maintain drug release during transportation as well as at the site of localization. This leads to a change in the distribution and further decreases drug clearance thereby increasing therapeutic efficacy and simultaneously reducing drug side effects (Yun *et al.*, 2013). The use of nanoparticles for protein delivery can also increase protein bioavailability due to their small size and large surface area (Rekha & Sharma, 2011).

In contrast to chronotherapy drugs, the use of nanoparticles as a strategy for drug delivery has not been developed significantly. Nanoparticles are potentially used in drug delivery because of their ability to link drug release to the molecular circadian rhythm of the desired cells. Therefore, effective chronotherapy delivery can be achieved based on the rhythm of the individual patient regardless of drug administration time (Ballesta *et al.*, 2017). This shows that the nanoparticle formulation containing the chronotherapy drug needs to be further developed.

The results of the strategies undertaken demonstrate their potential for use in CTDD systems. However, these strategies are not yet applicable in clinical practice because most trials are limited to *in-vitro* and *in-vivo*. In the *in-vitro* release test, several studies had differences in simulating colonic pH conditions. There is a need for the standardization of the *in-vitro* study methods for degradation and release tests as well as the *in-vivo* study for animal models. Therefore, the test results can be compared with other laboratories to achieve a better correlation with *in-vivo* conditions in humans. To be clinically relevant

and for commercial production, further studies, such as clinical trials in humans, are needed to confirm the efficacy and safety of the CTDD systems. The strategies for the systems that have been successfully investigated can also be applied to other drugs with similar characteristics.

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