

Challenge and Development Strategy for Colon-Targeted Drug Delivery System

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ABSTRACT

Colon-Targeted Drug Delivery System (CTDDS) is able to improve local therapeutic effects in the treatment of colon-specific diseases, such as Crohn's disease, Ulcerative Colitis (UC), and Irritable Bowel Syndrome (IBS). A colon can also be a suitable site for systemic delivery of drugs susceptible to extreme gastric pH, such as peptides and protein therapeutics. The physiological conditions of the gastrointestinal tract and the physicochemical properties of drugs are being considered to develop strategies and approaches to overcome emerging challenges. This review will discuss factors, challenges, strategies, and approaches to developing a colon-targeted drug delivery system.

Keywords: *colon-targeted; drug delivery system; colon disease; polymer*

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INTRODUCTION

Conventional medicine in treating various diseases has been carried out for a long time. They treat local intestinal disorders, such as ulcerative colitis, Crohn's disease, irritable bowel syndrome, chronic pancreatitis, colon cancer, and intestinal fibrosis. It is reported that intestinal fibrosis is initiated by severe and chronic tissue damage due to recurrent inflammation, as observed in Crohn's disease patients (Iswandana et al., 2020). However, several obstacles were found in the treatment process, such as the unspecified location of drug delivery, drug dose tended to be high, frequency of drug administration was frequent, decreasing drug bioavailability, and systemic side effects appeared. As a result, these barriers reduce the drug's effectiveness (Dugad, 2018), which is the main reason for developing Colon-Targeted Drug Delivery System (CTDDS).

CTDDS works locally with the aim that the drug works optimally. In addition, it can reduce the risk of systemic side effects. Two routes of administration are used, namely oral and rectal. The oral route is the primary choice by considering the patient's comfort and compliance in taking the drug. In addition, this route is safer than the rectal route, and the preparation process does not require sterile premises and equipment (Leuva, 2012). Moreover, advances in nutriology have suggested the colon as a superior site for nutrition absorption. Hence, the colon-targeted delivery system gives an emerging tool for functional food innovation (Feng et al., 2020)

The human digestive tract is very complex. In the development of this targeted colonic drug delivery system, several factors must be considered in this regard, namely colonic anatomy and physiology, colon pH, colonic transit time, colonic pressure, colonic enzymes and microbes, colonic pressure, the volume of fluid in the colon, viscosity substances in the colon, and colonic drug absorption (Amidon et al., 2015; Irianti et al., 2020).

Several designs have been used to develop a colon-targeted drug delivery system based on these circumstances. Initial methods include a pH-controlled system, time-controlled system, and microflora-controlled system. Then the design was further developed into a combined pH and microflora-controlled system, an intestinal pressure-controlled system, an osmotic-pressure controlled system, and a multi-particulate system (Philip & Philip, 2010; Anita, et al., 2019). This review will discuss the factors and challenges and the design and strategy based on the physiological condition of the colon and the physicochemical properties of the drug.

METHODS

This article reviews studies journals and articles from official sources related to the topics discussed. Articles and journals sourced from Science Direct and Scopus with search keywords are "Colon-Targeted Drug Delivery" and "Colon-Targeted Drug Delivery (based on strategy)". The data obtained were compiled, analyzed, and concluded to obtain conclusions regarding the literature study.

CTDDS Factors and Challenges

Anatomy and physiology

The human large intestine is 1,500 cm long, consisting of the cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. The colon's primary function is to absorb water and electrolytes. The colon absorbs about 600 ml of water per day, with about 2000 ml per day. The colon does not secrete any digestive enzymes because the entire process of digesting food by enzymes is completed before the chyme reaches the colon. There are significant physiological differences between the colon and other parts of the gastrointestinal tract. The colon's lumen is covered by mucus and does not have villi like in the small intestine. The colon has a natural flora that has various functions, such as increasing intestinal immunity, promoting colonic motility, helping to maintain the integrity of the colonic mucosa, and digesting small amounts of cellulose into short-chain fatty acids, which can diffuse passively and contribute nutrients (Sherwood, 2013). Pathological conditions, such as ulcerative colitis and Crohn's disease, can cause changes in the colonic mucosa, affecting the absorption of drugs.

Colonic pH

There are significant differences in pH in healthy humans along the gastrointestinal tract (Leuva, 2012). The illustration is shown in Figure 1. The food consumed and the pathological conditions in each individual can cause the pH to change slightly (Amidon et al., 2015). Consumption of carbohydrate-rich foods can cause the colonic pH to become more acidic due to the fermentation of carbohydrates by colonic bacteria. The fermentation process will produce short-chain fatty acids (SCFAs). SCFA will be absorbed and metabolized by the colonic epithelium, which causes a decrease in the pH value in the digestive tract. The fermentation process also occurs in lactulose for constipation patients, producing lactic acid. The pH condition was also noted to have decreased in patients with ulcerative colitis (Patole

& Pandit, 2018). This is an essential consideration in manufacturing colon-targeted preparations using pH-sensitive polymers (Amidon et al., 2015).

Enzymes and colonic microflora

Aerobic and anaerobic bacteria are found throughout the digestive tract, with the most significant number found in the colon. There are about 400 species with a concentration of about 1000 CFU/ml (Dugad, 2018). These bacteria produce enzymes that can metabolize drugs and some biomolecules. The following are some enzymes involved in developing a colon-targeted drug delivery system that can be seen in Table 1.

These considerations regarding the specific bacteria present only in the colon are used for several approaches in manufacturing colon-targeted drug delivery systems (Kotla et al. 2016). For example, the fermentation process carried out by colonic anaerobic bacteria on polysaccharides is used as a polymer in controlled release preparations. Other techniques, such as the biotransformation of some drugs into their active forms, carried out by azoreductase enzymes against azo bonds, have been found in prodrugs approaches (Ray, 2019).

Colon transit time

Colonic transit time is essential in the bioavailability of drugs explicitly administered to the colon. The movement of substances in the colon occurs very slowly compared to the rest of the gastrointestinal tract (Kang et al., 2012). Colonic transit time is determined mainly by drug administration, food in the gastrointestinal tract, and the type of preparation used. Some studies suggest that differences result from the different timing of drug administration in the morning and evening. This is because colonic motility occurs more slowly when the body rests. The type of preparation affects the difference in size. Smaller dosage sizes have a longer transit time than larger dosage forms (Amidon et al., 2015). Pathological conditions can also affect transit time in the colon. In UC patients, colonic transit time

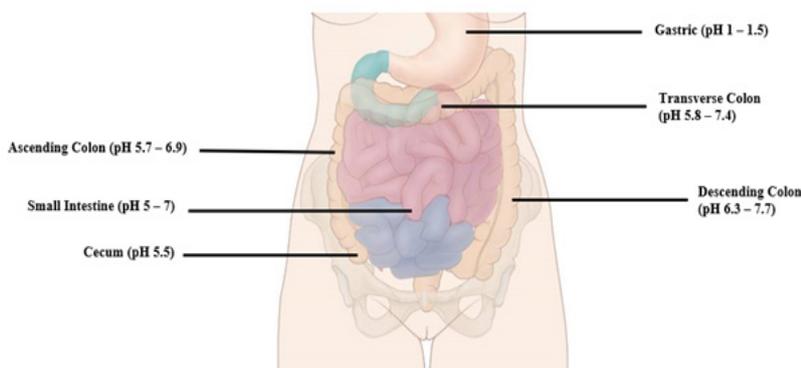


Figure 1. Anatomical and physiological features of gastrointestinal tract

Table 1. Drug metabolizing enzymes in the colon

Enzymes	Microorganism	Functions
Nitro reductase	<i>E. coli bacteroides</i>	Reduce nitro groups in aromatic and heterocyclic compounds
Azo reductase	<i>Clostridia lactobacilli</i> , <i>E. coli</i>	Reduce azo compounds
Esterase and Amidase	<i>E. coli</i> , <i>P. vulgaris</i> , <i>B. subtilis</i> , <i>B. mycoides</i>	Cut the ester group or amide group in carboxylic acids
Glycosidase	<i>Clostridia eubacterium</i>	Cut beta glycosidase in alcohol and phenol
Glucuronidase	<i>E. coli</i> <i>A. aerogenes</i>	Cut beta glucuronidase in alcohol and phenol

was approximately 24 hours faster than the average transit time in healthy humans, about 52 hours (Gupta et al., 2012).

Drug absorption in the colon

The colon has a narrower surface area than the small intestine because there are no villi on the mucous membrane (Rana et al., 2013). However, the substance's viscosity in the colon is higher than in other parts of the gastrointestinal tract because water absorption occurs along the colon. This affects the colonic fluid's drug dissolution process, determining the absorption process. The process of drug absorption in the colon occurs transcellular and paracellular. The transcellular process is carried out by lipophilic drugs in which drugs will pass through cells.

In contrast, the paracellular process is carried out by hydrophilic drugs. Drugs will pass through tight junctions between cells. Another factor affecting the function of drug absorption in the colon is the disease suffered by the individual (Dugad, 2018).

CTDDS Design and Strategy

pH controlled system

There is a change in the pH range throughout the human gastrointestinal tract caused by different physiological conditions. These different pH ranges are utilized to control the drug's release time from the system by coating the entire drug surface using a pH-sensitive polymer, which is insoluble in acidic pH but soluble in slightly alkaline or neutral pH (Ray, 2019). The characteristics of this polymer will protect the drug while in the upper gastrointestinal tract and delay its release until it reaches the colon. The drug-coating layer can be single-layered or multi-layered. One layer can be composed of the same polymer or two polymers. One of the polymers is a pH-

sensitive polymer. The multi-layered system comprises two polymers that can dissolve at different pHs (Dugad, 2018).

The most widely used pH-sensitive polymer is derived from polymethacrylate, namely Eudragit® (Leuva, 2012). The combination of Eudragit® L and Eudragit® S is most used. These polymers each have a different response to different pH conditions, so combining these two polymers in a specific ratio can optimize the dissolution rate (Amidon et al., 2015).

Oshi et al. evaluate the ability of preparations containing dexamethasone, which is one of the treatments for IBD. This preparation is coated with Eudragit® S100 on the outermost layer to prevent the drug from being released first in the upper gastrointestinal tract (Oshi et al., 2018). The results of *in vitro* tests using different pH values, namely 1.2, 6.8, and 7.4, showed that the system could protect the drug from sudden release at acidic pH and could control the slow drug release at alkaline pH (Sahle et al., 2017).

Apart from coating techniques that use solvents, it is also known as "dry coating" or compression-coating (tablet in-a-tablet). This technique uses dry excipients to coat the drug in the tablet compression process to overcome the problems that often arise in the coating process using solvents (Oshi et al., 2018).

Qiao et al. used electrostatic dry coating as a coating technique on ibuprofen tablets with Eudragit® L100-55. Attaching the dry powder that will coat the tablet is assisted by electrostatic forces and PEG 400 as a plasticizer solution. *In vitro* testing showed an increase in temperature and length of time in the curing process in the last stage of the process, thereby reducing the level of drug released at acidic pH (Qiao et al., 2013).

Efforts to prevent the early release of drugs in the upper gastrointestinal tract depend on the polymer layer's thickness in the drug coating process. Some studies recommend that the polymer coating be more than 10% w/w. or consists of many layers (multi-layered) (Qiao et al., 2013). In another study of 5-ASA, the coating used for the coating process was 18% ethyl cellulose and 28% Eudragit® S (Macleod et al., 1999). This process requires a longer time and longer stages of work. Nguyen et al. used a combination of zein and Kollicoat® MAE 100P to create a single-layered prednisolone tablet coating process. The formed layer was tested using SEM. The formula with a coating concentration of 8% had a homogeneous texture. The results of *in vitro* testing using dissolution media with different pH (1.2, 4.6, 6.8, and 7.4) showed that formulas with the same concentration could protect the drug during acidic pH and released immediately when it reached pH 7.4 (Xu et al., 2014).

Time controlled release system

The drug contained in the system is coated with a polymer that can control drug release according to a predetermined time. Discharge can occur immediately or slowly be released when it has reached the colon. The main factor that must be considered here is the transit time of the human gastrointestinal tract, which varies greatly depending on the type and amount of food consumed. The first product made using this system was Pulsincap®. The dosage form is in the form of a capsule containing a hydrogel and a drug in it. The capsule body is water-insoluble, the cap is water-soluble, and the entire capsule is coated with a special enteric polymer. The polymer will dissolve when the system enters the small intestine and the hydrogel's expansion. The amount of hydrogel used will determine the drug release from the system (Nguyen et al., 2019). The system was developed to be more complex through enteric-specific polymers and pH-sensitive polymers, more commonly known as enteric-coated timed-release press (ETP) tablets, to optimize the drug release process at the desired location. ETP consists of three general components: the drug as a core, a polymer having a timed-release specification, and a pH-sensitive polymer (Philip & Philip, 2010; Sahle et al., 2017).

Research by Handali et al. used a combination of Eudragit® FS30D as a pH-sensitive polymer and two time-controlled polymers, namely Eudragit® RL 30D and Eudragit® RS30D, for theophylline delivery as a model drug (Handali et al., 2018). *In vitro* testing used four dissolution media with different pH, namely pH 1.2, pH 6.8, pH 7.4 phosphate buffer, and pH 6.8, which indicates stomach pH, small intestine, after small intestine, simulated colonic pH, respectively. The formulation with a concentration of Eudragit® FS with a concentration of 50.03% and Eudragit® RS: RL = 2.56

showed the most optimal results, with 25.21% of the drug starting to release at pH 7.4 and as much as 50.78% of the drug being released at pH 6.8 (Chourasia & Jain, 2003; Singh et al., 2015; Lee, et al., 2020).

Another type of controlled time delivery system is pulsatile. Pulsatile is a drug delivery system that regulates drug release after the lag phase, which allows for chronotherapy treatment (Handali et al., 2018) and can also be used for a specific location, the colon.

Four characteristics of each polymer used in this system are rupturable, erodible, permeable, and semipermeable. Rupturable is a water-insoluble polymer, relatively permeable. The drug release process occurs after the lag phase due to hydrostatic pressure caused by swelling of the polymer or osmotic pressure caused by water entering the preparation. Erodeable is a hydrophilic polymer whose solubility does not depend on pH will swell when exposed to liquid, and the dissolution process or disintegration of the polymer will delay the drug to be released. Permeable is a water-insoluble polymer, where water from the gastrointestinal tract will be able to enter the preparation. The drug will diffuse out of the membrane after dissolving in the liquid (Maroni et al., 2010; Palugan et al., 2015).

Colonic Microflora Controlled System

Prodrug

A prodrug is the inactive form of the drug caused by covalent bonds between the drug and certain chemical compounds, such as polysaccharides, amino acids, and some types of polymers. Enzymes in the colon are needed to convert the inactive form of the drug to its active form. It can deliver drugs precisely to the colon (Maroni et al., 2013).

Prodrug of 5-ASA, a treatment for inflammatory bowel disease and ulcerative colitis, is made by forming an azo bond incorporating sulfapyridine, 4-aminobenzoyl-β-alanine, or 5-ASA to 5-ASA to form sulfasalazine, balsalazide, and olsalazine. The therapeutic effect produced by 5-ASA is determined by the rate of breaking of azo bonds, which is related to the presence or absence of azo reductase bacteria in the colon (Sardo et al., 2019). In addition to the azo bond, the 5-ASA prodrug can be formed by ester linkage upon incorporation with the polysaccharides dextran, cyclodextrin, hydroxypropyl methylcellulose (HPMC), chondroitin sulfate, and inulin; and amide bonds such as incorporation with chitosan (Maroni et al., 2013).

The type of polysaccharide used and the solubility of the prodrug affect the release of 5-ASA drugs in the colon. Dextrin-5-ASA is stable in the small intestine.

The drug can be released once it reaches the colon; in chitosan-5-ASA, there was no drug release; drug release cyclodextrin-5-ASA occurs in the stomach and small intestine but, to a lesser extent, released in the colon (Sousa et al., 2014). However, the toxicity, safety, and possible failure of bond cleavage due to disruption of the enzyme under pathological conditions have limited clinical trials on 5-ASA (Maroni et al., 2013). Use of chitosan in the prodrug system is used to manufacture metronidazole prodrugs. Metronidazole is linked to the amino group of glucosamine chitosan using two different spacers, namely glutaric and succinate. The results of *ex-vivo* testing showed that both prodrugs were stable at pH 1.2 and could release drugs when they were in the colon due to enzymatic processes, with glutaryl-prodrug having a slightly longer drug release time (Jain et al., 2017).

Biodegradable polymer

The microflora in the colon is dominated by anaerobic bacteria, such as Bacteroides, bifidobacteria, eubacteria, clostridia, enterococci, enterobacteria, and ruminococci. The process of fermenting undigested food in the stomach or small intestines, such as disaccharides, trisaccharides, and polysaccharides, requires an enzyme reaction produced by these bacteria. Enzyme reactions include glucuronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azo reductase, deaminase, and urea dehydroxylase. The presence of biodegradable enzymes in the colon causes biodegradable polymers in the colon-targeted drug delivery systems to be very suitable because they are more specific than other approaches (Philip & Philip, 2010; Dar et al., 2017).

One of the methods used is chitosan combined with polyacrylic acid to form a polyelectrolyte complex (PEC) in a hydrogel (Mura et al., 2011). Hydrogel is a collection of hydrophilic polymeric biomaterials, has a three-dimensional structure, and can hold large amounts of water. The hydrogel has a structure similar to biological tissue with a moisture content of 70–99%, which is capable and biocompatible in encapsulating hydrophilic drugs (Shah et al., 2011). PEC, in this case, is biodegradable and can expand (swelling) because it absorbs water at neutral and alkaline pH. The swelling process is helpful in drug release and distribution of the drug when it has been released in the colon. The results of *in vitro* testing with the involvement of the enzymes α -glucuronidase and α -glucosidase showed that the drug was released in the first 2 hours in higher quantities than *in vitro* tests without the involvement of enzymes. The presence of this enzyme also reduces the gel strength of the expanded polymer (Mura et al., 2011).

Bioadhesive polymer

Bioadhesive materials can hold the drug on the mucous membrane to prolong the contact time of the drug with

the colonic mucosa. This will help the absorption of the drug to be maximized (J. Li & Mooney, 2016), especially for drugs with poor absorption profiles to enhance the therapeutic effect. The most widely used bioadhesive polymers are hydrophilic polymers and hydrogels, with many carboxyl groups (Ahmad et al., 2012). Carbomer 940 (C940) is one of the excellent bioadhesive agents in holding drugs in the gastrointestinal mucosa. The use of combination with hydroxy propylene (HPC-H), a bio-adhesive material, produces a synergistic effect. The formed preparations are also resistant to media with high viscosity, such as the colon (Bakhru et al., 2013).

pH and Microflora Controlled Combination System

This approach uses a pH-sensitive polymer and a biodegradable polymer. As in the combination of pectin, polyethylene glycol-400 (PEG-40), methacrylic acid (MAA), and ammonium persulfate (PSA), with N,N methylene bis acrylamide (MBA) as a crosslinker to form pectin-g-(PEG-co-MAA). Pectin is an anionic polysaccharide derived from plants. It is commonly used for drug delivery to the colon because it can be destroyed by enzymes in the colon and is resistant to enzymes in the upper gastrointestinal tract (Wong & Nurjaya, 2008; Jain et al., 2015). MAA, a pH-sensitive polymer, has a carboxylic group that can be deprotonated at alkaline pH. It plays a vital role in the swelling process. This is closely related to the drug release process based on *in vitro* testing using three different pH. The drug releases up to 70% at alkaline pH of 7.4 (Mura et al., 2011).

Colon Pressure Controlled System

The colon has more significant pressure than the small intestine. This pressure assists the drug release process by disintegrating the water-insoluble polymer that coats the drug. The thickness of the polymer is an essential factor that must be considered in the manufacture of this system (Nguyen et al., 2019).

Pressure-controlled drug delivery capsules (PCDC) are prepared by coating ordinary gelatin capsules with a water-insoluble polymer, for example, ethyl cellulose. Tests of the system in delivering 5-ASA showed results that matched the success of the drug being absorbed at the appropriate time according to the location of the colon. However, human tests have shown premature release of the drug in the small intestine due to increased pressure generated by peristalsis (Nguyen et al., 2019).

Osmotic Pressure Controlled System

Initially, the osmotic pump tablet (OPT) consisted of a tablet core in the form of a drug covered with a semipermeable membrane, having an orifice on the surface of the drug, which was drilled. This is an elementary osmotic pump (EOP) and can only deliver water-soluble drugs (Abbasi et al., 2019).

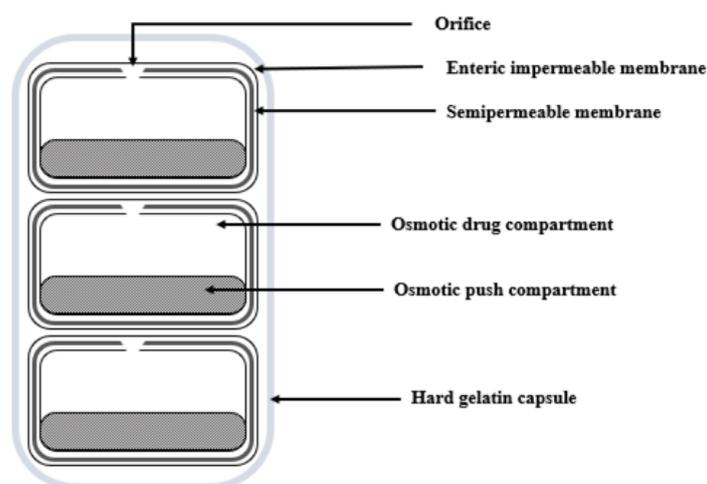


Figure 2. Osmotic pressure controlled system

In the next stage of development, to overcome the limitations of water-insoluble drug delivery, an OPT with two layers (bilayer) in the core was developed. One part is in the form of a drug compartment. The other part is a push-pull compartment that contains an osmotic agent and an expanding agent, known as a push-pull osmotic pump (Verma et al., 2002; Syed et al., 2015). The manufacture of the tablet core uses a tablet compression device with a punch equipped with a needle, then proceeds to the coating process without going through the stages of using a drill. The no-drill manufacturing step, meaning that there is no gap formation step on the surface of the drug compartment, was carried out because the side of the tablet is the side that is slightly sprayed during the tablet coating stage so that this gap can be helpful in the later drug release process (Sastry & Khan, 1998). However, this no-drilling stage has limitations if produced on an industrial scale (Liu & Xu, 2008). In the delivery of nifedipine powder which has low solubility, NaCl as an osmotic agent, PVP K90 as a suspending agent, CMC-Na as an expanding agent, and ethyl cellulose and PEG 400 as a semipermeable membrane, the delivery was successfully carried out by the nifedipine release process lasting for 24 hours. There was no significant difference in the drug release process in different media on *in vitro* testing. This proves that the drug release process does not depend on the physiological state of the digestive tract (Sastry & Khan, 1998).

Using this system for colon-targeted drug delivery, known as an osmotic-controlled release oral delivery system targeted colon (OROS-CT), may consist of one or more units covered with a hard gelatin capsule. The illustration of the system is shown in Figure 2. Gelatin, which is the outermost layer, will dissolve as soon as the preparation comes into contact with liquid in the gastrointestinal tract, which prevents fluid from entering the preparation

belonging to a special enteric polymer. Enteric-specific polymers that are acid-resistant will begin to dissolve when the gastrointestinal tract has entered a higher pH in the small intestine. Then, the water enters through the semipermeable membrane, which causes the expansion of the propulsion compartment (Abbasi et al., 2019). At the same time, the most commonly used enteric polymer is Eudragit. In the use of Eudragit® L100 for the delivery of dicyclomine hydrochloride, which is one of the treatments for IBS, it is proven that this system can release drugs at pH 7.4, which is a simulation of colonic physiology (Liu & Che, 2006; Verma et al., 2012).

Multi-particulate System

CTDDS using a multi-particulate approach is smaller than ordinary systems, such as beads, pellets, and granules. This approach aims to increase drug bioavailability dosage stability, use lower doses, and minimize systemic side effects (Chaudhary et al., 2011; Bethel et al., 2020). This is reinforced by the ability of multi-particulate preparations to reach the colon faster, easier, and last longer in the colon (Deshmukh et al., 2020). Considerations regarding the pH gradient along the gastrointestinal tract and specific microflora in the colon are utilized for site-specific delivery (Sinha & Kumria, 2003). The preparation of microparticles using the ionic gelation technique using amidated pectin, then coated with Eudragit® S100, succeeded in delivering sulfasalazine to the colon without being destroyed in the stomach & small intestine. The release occurred more optimally in the test using the rat cecal content (RCC), proving microbes' role in the colon (Chaudhary et al., 2011).

Another multi-particulate preparation is pellets. Pellets are spherical or pseudo-spherical in shape with a smooth surface ranging from 500 to 1500 m and have a reasonably high density and reasonable flow rate (Asghar

& Chandran, 2006; Palugan et al., 2015; Singh et al., 2012). Pellets are usually given in capsules or tablets, released when they have reached the gastrointestinal tract with a dose that must be evenly distributed in each unit (Politis & Rekkas, 2011). The provision of pellets has also developed by modifying it with a matrix or reservoir system. In the matrix system, the active substance will be dispersed in the excipients, while in the drug reservoir system, it is in this part where one or more layers will coat the core. The application of pellets in CTDDS involves the adjustment of polymers that encapsulate the drug core. Taking the drug release process into account, the administration of the polymer can be based on pH in the gastrointestinal tract, microbes in the colon, or transit time (Palugan et al., 2015). The use of biodegradable polymers, for example, in the combination of pectin and ethyl cellulose in coating pellets containing 5-fluorouracil (5-FU), showed increased drug release when rat cecal contents (RCC) were present compared with no RCC (Gazzaniga et al., 2006; Bose et al., 2014; Hua, 2020).

In the use of Eudragit® S combined with Eudragit® L, which is a pH-sensitive polymer, the preparation was proven to withstand drug release during testing at pH 1.2 and 6.5 and only released at pH 6.8 and 7.2 (Wei et al., 2008). The combination of a pH-sensitive polymer, namely Eudragit® L100, and a biodegradable polymer, namely chitosan, in the delivery of prednisolone pellets showed that the drug did not release at acidic pH and drug release increased with the presence of enzymes in the colon (Akhgari et al., 2005; Gangurde et al., 2013).

Another type of multi-particulate is beads. Beads can control drug release and increase drug bioavailability by stabilizing the drug before it reaches the colon (Kaur & Kim, 2009). Polymers commonly used to form beads include chitosan, alginate, and pectin. In the delivery of tetrandrine one of the treatments for intestinal fibrosis, beads are formed from chitosan with a crosslinker in tripolyphosphate by the ionic gelation method (Iswandana et al., 2017a). Then proceed with the coating process with various pH-sensitive polymers. The *in vitro* test results showed that the system was able to withstand drug release well until it reached a simulated colonic pH condition, which is 6.8, with the most optimal results indicated by a system coated with cellulose acetate phthalate (phthalate polymer) because it can release more drugs than the conventional system coated with Eudragit (methacrylate polymer) (Sanli et al., 2007). In another formulation, the use of calcium alginate and calcium pectinate to form beads coated with cellulose acetate phthalate showed promising results in protecting the drug during the upper gastrointestinal tract and drug release process in simulated colonic conditions (Iswandana et al., 2018; Iswandana et al., 2017b).

Future Perspective

The development of a targeted colonic delivery system was carried out by considering two important aspects: the physiological condition of the human gastrointestinal tract and the physicochemical properties of drugs. Physiological disorders in the form of changes in pH along the gastrointestinal tract, food transit time, and enzyme secretion in the colon became the basis for the development of the system using pH-sensitive polymers, time-controlled polymers, and biodegradable polymers separately. Then an obstacle arose in releasing the drug from the system, so a combination of all three polymers was used in one delivery system.

Combining these three polymers has good potential in delivering drugs to the colon based on *in vitro* testing. However, the non-uniform results in several tests indicate that this system still needs to be developed and evaluated, especially at some critical points, which often differ between researchers. We need a standard that researchers can use regarding the optimal delivery system based on certain conditions and validation of the manufacturing process to ensure that each product produced has uniform characteristics. For further development, especially the use of this system as a treatment, it is necessary to test the effectiveness and safety in humans, especially for strategies in the form of a combination of techniques.

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