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Review Article

AN OVERVIEW: DEVELOPMENT OF COLON DRUG DELIVERY SYSTEM AND ITS APPLICATION AND LIMITATIONS

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ABSTRACT

There are various routes of drug administration. Oral administration is considered the most preferred route in drug administration for systemic effects, but the oral administration is not suitable for people with ulcerative colitis, crohn's disease, bowel cancer, diarrhea, treatment of diseases that sensitive to circadian rhythms such as asthma and angina, as well as for steroids administration. The delivery of targeted drugs has the goal of achieving the desired therapeutic profile by delivering the drug to the target site. This study conducted by reviewing related articles based on specify keywords on Science Direct database that has been published for the last 10 y. In recent decades, research has been conducted to develop methods that can target drugs to specific organs. The focusing on targeted drug delivery system to the colon, the various ways that were carried out for its approach, as well as the evaluation. By this study, some challenges in the colon drug delivery system could be overcome along with new approaches.

Keywords: Colon drug delivery system, Colon cancer, Nanoparticles, Colon targeted drug delivery

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INTRODUCTION

Over the past few decades, research has been conducted to develop methods that can target drugs to specific organs. Targeted drug delivery has the objective of achieving the desired therapeutic profile by delivering the drug to the target site [1]. One of the concerns is the drug delivery system to the large intestine (colon). The colon is referred to as the optimal place of the absorption of proteins and polypeptides after oral administration due to the relatively low activity of proteolytic enzymes and a sufficiently long transit time in the colon [2]. A large number of polysaccharides such as pectin, amylose, guar gum, chitosan, inulin, cyclodextrin, chondroitin sulfate, detraction, and dextrin have been identified for their use for targeted drug delivery system in the colon [3].

Targeted drug delivery to the colon is used to deliver substances that can be degraded by digestive enzymes in the stomach such as proteins and peptides. It is also used for the treatment of various diseases such as ulcerative colitis, crohn's disease, bowel cancer, diarrhea, treatment of diseases that sensitive to circadian rhythms such as asthma and angina, as well as for steroids administration and others [4]. Targeted drug delivery systems in the colon have to overcome some challenges, such as preventing the release of drugs in the stomach and small intestine, along with establishing trigger mechanisms in the delivery system that are responsive to physiological changes in the colon [5].

In targeted drug delivery systems to the colon, the release and absorption of drugs should not occur in the stomach as well as the small intestine and bioactive agents should not degrade at any dissolution sites yet only released and absorbed once the system reaches the colon. Currently, targeted drug delivery systems to the colon is a challenging problem in the field of pharmaceutical technology [6].

There are some advantages of the drug delivery system to the colon, such as fewer systemic side effects, a suitable place of absorption for protein and peptide drugs, as well as minimizing mucosal irritation [7]. In most cases, the dosage of the drug can be reduced. This is because the drug is sent directly in whole form to the target place [4]. Small frequency of dosing could improve patient compliance as well as lower the cost. colon drug delivery system (CDSS) is used for the treatment of inflammatory bowel diseases such as ulcerative colitis, crohn's disease, and other diseases [8]. Another advantage is the high retention time so that it increases the bioavailability of drugs that are difficult to absorb and minimizes the first pass effect. When the dose is administered orally, it must pass through the pH range and enzyme, before reaching the target site, which complicates the bioactivity of the drug and the efficiency of drug delivery [9, 10]. Targeted drug delivery to the colon reduces systemic side effects and improves the absorption of drugs that cannot be absorbed properly due to the high retention time of the colon [8]. In addition, it may increase the systemic bioavailability of poorly absorbed drugs due to the long retention time in the colon [11].

However, there are shortcomings of the drug delivery system in the colon, such as there are some incomplete manufacturing steps and drugs release [8]. In the colon, there is microflora that can affect the performance of the colon. Another limitation is that cytochrome enzymes (p450) enzymes have a lower affinity in the colonic mucosa [7] as well as the lack of a proper dissolution method to evaluate *in vitro* dosage forms [12].

MATERIALS AND METHODS

The study of this article review is carried out by searching for some literature and then the data is extracted based on its criteria. Keywords were compiled consisting of colon drug delivery system, colon targeting, and colon cancer in the search column of the Science Direct database. The literature is selected according to the inclusion criteria, that is, literature that discusses the drug delivery system in the colon, the evaluation, the polymers used, the various approaches taken, and articles published for the last 10 y. As for the exclusion criteria, that are articles that do not fit the topic of discussion and full paper that cannot be accessed.

RESULTS AND DISCUSSION

Mechanism of drug release and drug absorption in general

There are several mechanisms by which drug release can be controlled in a system. In the development and manufacture of a controlled release system, it is important to understand the mechanisms that occur. A controlled energy source is necessary for the system to control the drug's release at the right time. There are also chemical and biological mechanisms to control the spatial release of drugs, namely partitioning, diffusion, osmosis, erosion,

and targeting. Partitioning is a very important mechanism that can control the delivery of drugs. Partitioning is a process by which solute molecules (such as an active substance) are dissolved in a solvent carrier. The process of dissolving the active substance involves transfer of drug molecules or ions from its solid phase to the surrounding medium (such as water, tissue or polymers). The next process is diffusion. Diffusion is the process of transferring the molecular mass of a substance from one part of the system to another. Then, osmosis occurs. Osmosis is a condition when solvents are transferred through a semipermeable membrane for diluting the solution containing solutes and solvents. Then, there is a process of erosion. Some polymers used as additives in drugs will experience erosion when undergoing a chemical reaction and then release the active substance [13].

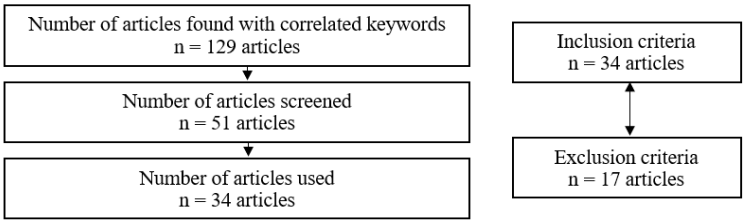

Fig. 1: Flowchart represent the literature search process

Release profile in the colon

Table 1: Release profiles in the colon

Colonic pH			Transit time	References
Asenden	Transversum	Desenden		
6.4	6.6	7.0	20–35 h	[8]

Criteria for drugs as colon drug delivery systems (CDSS)

The best candidates for CDDS are drugs that show a poor absorption effect on the stomach or intestines. Drugs used in the treatment of inflammatory bowel disease (IBD), ulcerative colitis, diarrhea, and colon cancer are ideal candidates for targeted drug delivery to the colon. The criteria for the selection of the drug as CDDS are summarized in table 2. Drug carriers are one of the factors affecting CDDS. The selection of drug carriers depends on the drug properties as well as the disease. Various physicochemical factors of the drug, such as chemical properties, functional groups of drug molecules, stability, drug partition coefficient, and the type of absorption enhancer selected, also influence the selection of carriers [6].

Table 2: Criteria for drugs as colon drug delivery systems (CDDS)

Criteria	Pharmacology classification	Non-peptide drugs	Peptide drugs	Reference
Drugs used for the local effect on the colon against gastrointestinal tract diseases	Anti-inflammatory drugs	Metoprolol, Nifedipine, Oksiprenolol	Oligonucleotides, amylin	[14]
Poorly absorbed drugs in the upper gastrointestinal tract	Antihypertensive, antianginal drugs	Isosorbid, Ibuprofen, Theophylline	Cyclosporine, Desmopressin	[14]
Treatments for colon cancer	Antineoplastic drugs	Pseudoephedrine	glucagon, epoetin	[10, 15]
Drugs that undergo extensive cross-first metabolism	Nitroglycerin and corticosteroids	Nicotine, Bleomycin	Sermorelin, Saloatonin	**[8]**

Approaches to drug delivery systems for colon

Delivery of pH-sensitive polymer-coated drugs

The theory is to provide a polymeric coating on the preparation with various pH-sensitive polymers that will result in delayed-release formulations and protect them from the degradation of the upper gastrointestinal tract. pH-sensitive polymers are insoluble in low pH and will become more soluble when the pH increases. The most commonly used polymer is the methacrylic acid copolymer, commonly known as Eudragit S. This polymer shows insolubility at low pH levels but becomes more and more soluble as the pH rises [11, 16]. During transit in the gastrointestinal tract, the pH varies from 1 to 8 and decreases significantly from the ileum to the large intestine. There are several problems related to this approach, namely: gastrointestinal pH variability between individuals is affected by diet and disease conditions, poor location specificity (begins to dissolve even in the lower small intestine).

Table 3: Polymers in the delivery of pH-sensitive polymer-coated drugs

Polymer	Optimum pH for dissolution	Reference
Polyvinyl acetate phthalates (PVAP)	5.0	[11, 17]
HPMC 55	5.4	[11, 17]
methacrylic acid copolymer, type A	≥6.0	[11, 17]
Eudragit FS30D	>7.0	[11, 17]
Hydroxypropylmethylcellulose phthalates (HPMCP)	≥5.5	[11, 17]
Methacrylic acid copolymer, Type C (Eudragit L100-55)	>6.0	[11, 17]
Eudragit FS 30D	6.8	[11, 17]
Methacrylic acid copolymer dispersion (Eudragit L30D-55)	>5	[11, 17]
Cellulose acetate trimetholiate (CAT)	5.5	[11, 17]
Hydroxypropyl methylcellulose acetate succinate (HPMCAS)	≥6.0	[11, 17]
Shellac (MarCoat 125 and 125N)	7.0	[11, 17]
Methacrylic acid copolymer, Type B	≥7.0	[11, 17]

Delayed release drug delivery system

The targeted delayed-release drug delivery system to the colon is achieved by extending the lag time. Transit time will be responsible for the delayed drug release. However, there are several disadvantages of this system, namely: [6, 8].

- Gastric emptying time and amount of food intake vary greatly between individuals.
- Peristalsis or contraction movements in the gastrointestinal tract can result changes in the transit of the drug in the gastrointestinal tract.
- Accelerated transit through different regions of the colon has been observed in patients with IBD, carcinoid syndrome, diarrhea and ulcerative colitis.

Drugs triggered by microbes' delivery system

This system is based on the specific enzymatic activity of the microflora on the colon. Colonic bacteria are mostly anaerobic and secrete an enzyme. The number of bacteria in the colon is much higher by about 10-11 CFU/ml [12]. The enzymes present in the colon, namely: [14, 18, 19]. Reducing enzymes: nitroreductase, azoreductase, N-oxide reductase, sulfoxide reductase, hydrogenase, hydrolytic enzymes: esterase, amidase, glycosidase, glucuronidase, sulfatase.

Table 4: Characteristics of various biodegradable polymers for targeted drug delivery to the colon

Polysaccharide	Information	Bacterial species that degrade polymers	Reference
Amylose	Excipients in tablet formulations	Bacteroides, bifidobacterium	[14, 18]
Arabinogalakton	Natural pectin; hemicellulose used as a thickening agent	Bifidobacterium	[1, 18]
Dekstran	Plasma expanders	Bacteroides	[14, 18]
Guar gum	Palactomannan is used as thickening agent	Bacteroides, ruminococcus	[14, 18]
Inulin	Polysaccharides consisting of a mixture of oligomers and polymers	Bifidobacterium	[14, 18]
Chitosan	Deacetylated chitin is used as an agent that improves absorption	Bacteroides	[14, 18]
Chondroitin sulfate	Mucopolysaccharides contain sulfate esters in position 4 or 6	Bacteroides	[14, 18]
Pectin	thickening agents	Bacteroides, bifidobacterium, eubacterium	[19]
Cyclodextran	Solvent agent of the drug and absorption enhancer.	Bacteroides	[14, 18]
xilan	Hemicellulose	Bacteroides	[14, 18]

Since biodegradable enzymes are only present in the colon, the use of biodegradable polymers for the delivery of drugs targeted to the colon is a more specific approach than other approaches [6]. Biodegradable enzymes can degrade polymers used as target drug delivery to the colon. Different polymers are used to prevent the release of the drug in the stomach and small intestine. When the coated formulation reaches the intestine, the biodegradable polymer will be degraded by enzymes produced by the microbial flora and the drug is released in the targeted organ [8].

Prodrug approach

The prodrug approach is used to mask undesirable drug properties such as bioavailability, less specific location, and chemical instability. The targeted prodrug approach is a strategy for directed and efficient drug administration, for example, by targeting specific enzymes. Glycoside derivatives are hydrophilic and poorly absorbed in the small intestine. However, when it reaches the colon, it will be effectively freed by bacterial glycosidase to release the drug and facilitate absorption by the colonic mucosa [14].

Polysaccharide-based delivery system

Polysaccharide-based delivery systems are another form of drug delivery system triggered by microbes. Polysaccharides are broken down by microflora in the colon into simple saccharides [6].

New approaches colon drug delivery system

Pressure-controlled drug delivery system

The digestive process occurs due to the contractility of the stomach and the peristalsis of the intestine. The contractility movement of the stomach results in the breakdown of particles becoming smaller and then transferred to the intestines. The peristalsis movement of the intestine is responsible for the passage of the bolus from one part of the gastrointestinal tract to the next. The peristalsis movement of the colon ascendens transfers the bolus to the transverse colon is called mass peristalsis. This peristalsis occurs in limited quantities, which is three to four times a day. This peristaltic movement of the intestine produces an increase in luminal pressure. Increased luminal pressure is key in the development of pressure-controlled drug delivery systems. The pressure-controlled drug delivery system consists of capsules containing the drug [20, 21].

Gelatin capsules are coated with a water-insoluble polymer such as ethyl cellulose on the inside. Water from the contents of the intestine is absorbed, thereby increasing the viscosity, which will increase the pressure in the capsule. The pressure in the capsule secretes the drug into the colon. The thickness of the ethyl cellulose membrane is the most important factor for the disintegration of the formulation. The system can be modified to hold and break at different pressures by changing the capsule size and capsule shell thickness [6].

Table 5: Examples of prodrug systems in CDDS

Medicine	Carrier	Hydrolyzed Linkages	Reference
5-aminosalicylic acid (*5-ASA)*	Azo conjugate	Linkage azo	[8]
Salicylic acid	Amino acid conjugates, glycine	Linkage amide	[8]
Dexamethasone	Carrier saccharide	Linkage glycosides	[8]
Fludrocortisone, hydrocortisone, prednisolone	Glucose, galactose	Linkage glycosides	[8]

Table 6: Polymers used in polysaccharide-based delivery systems [8]

Classification	Example	Reference
Disaccharides	Lactose, maltose	[8]
Oligosaccharides	Cyclodextrin, lactulose, raffinose, sachyose	[8]
Polysaccharide	Alginate, amylose, cellulose, chitosan, starch, chondroitin sulfate, pectin, xanthan gum	[8]

CODES™

CODES™ is a new technique developed to address the weaknesses of pH and time-dependent drug delivery systems. This method was developed by utilizing lactulose which acts as a trigger for the release of specific drugs in the colon. The CODES™ system consist of a tablet core containing active ingredients coated with acid-soluble polymers such as Eudragit E and then coated with enteric materials, such as Eudragit L. Enteric polymers protect the system inside the stomach until the system is sent to the small intestine. The higher pH of the small intestine makes the enteric layer begin to dissolve. In the colon, lactulose begins to dissolve with the help of sufficient acidic media-producing microflora and is able to dissolve the acid layer that surrounds the drug and affects the rate of dissolution of the drug [22].

Osmotic controlled drug delivery system (OROS-CT)

The mechanism of release of the drug is that the gelatin capsule contains a thrust-pull unit dissolved after ingestion. The system is covered with an impermeable membrane that resists the release of the drug at the acidic pH of the stomach. Then, in the higher intestinal pH of pH>7, the semipermeable membrane begins to dissolve and water enters which causes the osmotic compartment to swell and creates a gel that can flow in the drug unit. Osmotic swelling of the thrust unit forces the drug gel out of the hole and the release of the drug begins when the unit reaches the colon. OROS-CT units can maintain a constant release rate of up to 24 h in the colon [14, 22].

Pulsatile drug delivery system

Pulsincap system

In this system, the formulation is developed in the form of capsules. The stopper is placed in the capsule to control the release of the drug. A hydrogel that can expand is used to seal the contents of the drug. The capsule swells when it comes into contact with the dissolution fluid and after a pause, the stopper is pushed out of the capsule and the drug will be released. Polymers such as hydroxypropyl methylcellulose (HPMC), poly methyl methacrylate, and polyvinyl acetate are used as hydrogel plugs. The lag time is controlled by the length and point of intersection of the plug in the capsule body [11, 23].

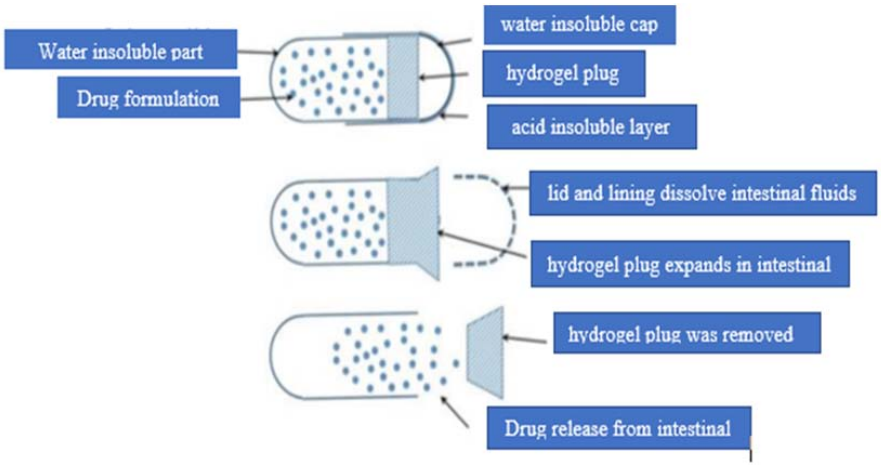

Fig. 2: Hydrogel system [11, 23]

Port system

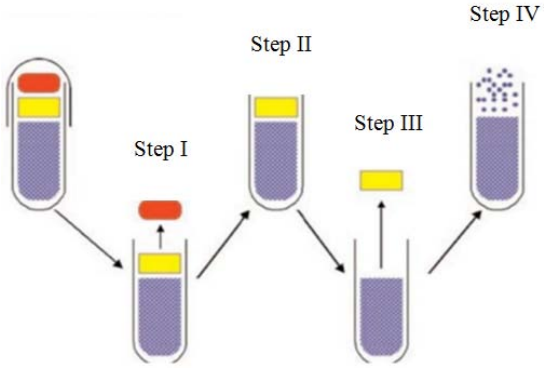

Fig. 3: Drug release mechanism system port [6]

The system is based on the theory of delayed release of the drug. The system consists of gelatin capsules coated with semipermeable membrane material (e. g., cellulose acetate), insoluble plugs (e. g. lipidic), and osmotically active agents along with drug formulations [12]. Moment the capsule comes into contact with the dissolution fluid; the semipermeable membrane allows the flow of fluid into the capsule resulting in a pressure swelling in the capsule body that causes the release of the drug due to removing the stopper. The drug will be released periodically with a lag time between successive intervals [6].

Azo hydrogel

The tissue materials that are capable of absorbing water but insoluble are formed by two mechanisms that are the covalent crosslinking of linear hydrophilic polymers and heterogeneous polymer mixtures. While in the digestive tract, the hydrogel will swell due to increased pH. This swelling of the hydrogel seperates the crosslinks in the hydrogel tissue causing the release of drugs trapped in the hydrogel. This hydrogel is prepared with cross-linker polymerization of N-substituted (meth) acrylamide, N-tert-butyl acrylamide and acrylic acid with 4.4-di (methylamine) azobenzene as a crosslinking agent. Some examples of polymers used are inulin, polyvinyl alcohol, guar gum, and dextran [8, 24].

Microsystems and nanosystems

Microparticles are spherical particles with a diameter of 1-1000 μm while the term nanosystem usually refers to a group of formulations with a size not greater than 100 nm [17, 25]. Micro/nanocarriers have several advantages, for example, increasing the volume/surface ratio, thus allowing the drug to have a higher contact area at the same dose and making drug delivery more effective. This can reduce the side effects and toxicity of the drug. Various methods have been developed to encapsulate drugs/proteins in polymer micro/nanoparticles, where double emulsions are the most widely used technique. Other encapsulation methods are single emulsion, phase separation (coacervation),

ultrasonic atomization, spray-drying, and mycolfluides [26]. Microencapsulation and nano-encapsulation are methods by which nano carriers, nanoemulsions, or bioactive molecules are collected in polymer shells. Encapsulation provides strong protection against gastrointestinal conditions, improving the solubility, transport, and distribution of hydrophobic compounds [27]. Nanocapsules have shown good loading capacity when used to improve mucosal delivery of highly hydrophobic drugs [28].

Table 7: Polysaccharide-based nanocarriers

Polysaccharide	Carrier polymers/materials	Mechanism	DNS categories	Description	Reference
Alginate	amphiphilic 4-aminothiophenol-modified from sodium alginate derivatives	chemical modifications; cross-linking	nanospheres	sensitivity and reduction response are good	[29]
Hyaluronic acid	amphiphilic hyaluronic acid-desilamina conjugate	chemical modifications	nanoparticles	increased cellular absorption, higher anti-inflammatory effect, targeted delivery, biocompatibility	[30]
Inulin	carboxymethyl inulin; 4-aminothiophenol	chemical modifications	nanoparticles	targeted delivery; pH/redox responsiveness; mucin adsorption; anti-colitis effect is better	[31, 32]
	inulin and hydrophobic hydropeptides	chemical modifications	nanoparticles	release of enzyme responses; good biocompatibility	[33]
Chitosan	chitosan and whey protein	electrostatic interaction	nanoparticles	increased cellular absorption; nickel-induced cytotoxicity inhibition; increases anti-inflammatory and antioxidant activity; epithelial barrier protection	[34]
	chitosan and ginger extract	electrostatic interaction	nanoparticles	Good stability in acidic and alkaline media	[1, 25, 35]
Chitosan and alginate	chitosan, alginate, and polystyrene nanoparticles	electrostatic interaction	nanocapsules	great stability; high cost; high encapsulation efficiency; stable release properties	[1, 25, 35]
Chitosan and hyaluronic acid	hyaluronic acid, chitosan and poly (D, L lactide-co-glycolide) and bovine serum albumin	chemical modifications; Electrostatic interaction	nanoparticles	targeted delivery; strong cell absorption ability; inflammatory inhibition	[36, 37]
Chitosan and pectin	double-layered pectin/chitosan and hydroxide	co-precipitation method; Electrostatic interaction	nanocompo-site beads	targeted drug delivery to the colon; increased mucosal adhesion; good resistance to pH changes	[19, 38]

*DNS: drug nanodelivery systems

Drug delivery based on multiparticulate system

Formulations of the multiparticulate approach are pellets, granules, microparticles, and nanoparticles. Since its particle size is smaller compared to the single-unit dosage form, the system is able to pass through the gastrointestinal tract easily. In addition, the multiparticulate system allows the drug to reach the large intestine quickly and is retained in the colon for a long time. A more uniformly dispersed multiparticulate system in GIT results in a more uniform absorption of drugs [8]. The system can also reduce the risk of systemic toxicity, local irritation, and predictable gastric emptying [12].

Colon drug delivery evaluation

Evaluation *in vitro* evaluation

There is no standardized evaluation technique available for CDDS (Colon-targeted drug delivery system) evaluation. As an *in vitro* model, it must have *in vivo* conditions of the gastrointestinal tract such as pH, volume, bacteria, enzymes, enzyme activity and ideal food components. This condition is affected by diet and stress. *In vitro* evaluation of the targeted drug delivery system in the colon are *in vitro* dissolution studies and *in vitro* enzymatic assays [8].

***In vitro* dissolution test**

Dissolution testing is carried out using conventional basket methods. Dissolution testing is carried out in different buffers. The media used for targeted drug delivery dissolution tests in the colon are pH 1.2 to simulate gastric juices, pH 6.8 to simulate the small intestine, and pH 7.4 to simulate the colon. The targeted drug delivery system to the colon was tested 2 h in HCl 0.1 N as well as 3 h in phosphate buffer pH 6.8 and pH 7.4 phosphate buffer [39, 40].

***In vitro* enzymatic assay**

There are two tests for *in vitro* enzymatic tests, namely:

a. The carrier drug system is incubated in fermentors containing a medium suitable for bacteria. The amount of the drug released at a certain time interval.

b. Studies of the drug release were carried out in a buffer medium containing the enzymes pectinase, dextranase or rat, guinea pig, and rabbit cecal impaction. The amount of drug released in a given time is directly proportional to the rate of degradation of polymer-carriers [8].

Evaluation *in vivo*

CDDS *in vivo* evaluations are performed on dogs, pigs, or mice because their anatomy, physiological conditions, and gastrointestinal microflora resemble humans. In addition, the distribution of various enzymes in the gastrointestinal tract of mice and rabbits is comparable to humans.

a. γ-scintigraphy is an image modality that allows the *in vivo* performance of the drug delivery system to be visualized under normal physiological conditions in a non-invasive manner. Through scintigraphy imaging, information can be obtained regarding the performance of colon-specific drug delivery systems in the human GI tract [17].

b. Roentgenography is a technique that involves combining non-drug opaque radio materials such as barium sulfate visualized by taking abdominal X-rays after oral administration. It is likely aimed at observing the movement, location, and integrity of the dose after

oral administration by placing the subject under a fluoroscope and taking a series of X-rays at various time intervals [39, 41].

Limitation of colon drugs delivery system

Colonic drug delivery has limitations similar to other methods of drug delivery, such as:

- Only for medications that are anticipated to have an effect on the colon;
- The use of polymers necessitates exact testing, and occasionally more is required;
- The patient's diet has a significant impact on the delivery process, which makes it possible for individual results to vary substantially.
- Some polymers are damaged by digestive enzymes and medication metabolizing enzymes.
- The preparation method's dependability is also subpar.

The distribution of this medication needs to be improved, nevertheless, due to the possibility of colon-specific diseases that can also be administered systemically.

CONCLUSION

The targeted drug delivery system to the colon has many advantages in the form of fewer systemic side effects, where absorption is suitable for protein and peptide drugs, minimizing mucosal irritation, less frequency of administration so as to lower costs, avoid the first-pass effect, and others. However, targeted drug delivery system to the colon must be ideal and be able to overcome various challenges, such as preventing the release of drugs in the stomach and small intestine, handling microflora that can affect the performance of the colon, lower cytochrome enzyme affinity (p450) in the colonic mucosa, and the lack of proper dissolution method to evaluate the dosage form *in vitro*. There are main approaches and new approaches in the use of colon drug delivery systems related to the polymers used to obtain maximum results.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest in this article.

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