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A critical review on formulation and evaluation of colon targeted drug delivery systems

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Abstract

A multidisciplinary scientific field that is fast growing is nanotechnology, often known as molecularly generated systems and technologies. Nanotechnology is a rapidly expanding field of applied science and engineering. It relies upon the concept of nano-scale manipulation of matter, meaning the ability to handle materials on a microscopic scale. Nanoparticles can be used to deliver a variety of substances, including conventional drugs, recombinant proteins, vaccines, and more recently nucleotides. Nanoparticles and other colloidal drug delivery techniques change the kinetics, body distribution, and drug release of a related drug. The treatment of negative effects and the distribution of therapy that targets certain tissues or cells are additional effects. As a result, nanoparticles in the pharmaceutical and biotechnology industries boost the therapeutic index and provide solutions to impending delivery problems for new classes of so-called biotech medicines such recombinant proteins and oligonucleotides.

Keywords: Nanoparticles; Colon; IBD; CDDS (Colon targeted drug delivery systems); Time-controlled release system (TCRS)

1. Introduction

The colon, the last portion of the digestive tract, is a 4 1/2-foot-long tube. The stomach and small intestine are where you digest the majority of your food. The cecum, located in the lower right corner of the abdomen, is where residual material enters the colon or big intestine. [1] The digested material then passes through the descending colon, the transverse colon, and the ascending colon before arriving at the sigmoid colon, which is located in the lower left area of the belly. The intestinal contents travel through the colon in between 18 and 36 hours; during this time, most of the water is absorbed and the few residual nutrients are grabbed into the circulation, resulting in solid fecal waste. [2] A layer of epithelial cells lines the colon's smooth interior when it is in good condition. A circular muscle that surrounds the colon and three lengthy muscles that run the whole length of the tube make up the two muscle groups that make up the colon's wall. [3] The numerous small penetrating arteries that go through the colon's muscular wall and deliver blood to its inner layer of epithelial cells are a large element of the colon's supply of blood, which is necessary for all tissues. [4]

For patients, the oral route of medicine delivery is seen to be the most practical. Depending on the physicochemical characteristics of the medication, oral administration of traditional dosage forms often dissolves in the stomach fluid or intestinal fluid and absorbs from these areas of the GIT. [5] It is a significant disadvantage when medicine needs to be shielded from the harsh environment of the upper GIT or when localized drug delivery is necessary for the colon. There

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are several benefits to using dosage forms that carry medication to the colon rather than the upper GIT. [6] When treating colon disorders such as Chron's disease, ulcerative colitis, carcinomas, and infections, oral medication administration to the colon can produce high local concentrations while reducing adverse effects brought on by drug release into the upper GIT or unneeded systemic absorption. [7] Due to the colon's abundance of lymphoid tissue and the quick local generation of antibodies triggered by antigen absorption by colonic mucosal mast cells, vaccine administration is made more effective. Interest is growing in the colon as a potential target for increased bioavailability of poorly absorbed medicinal molecules. A dependable colonic drug delivery system may also play a key role in the colonic absorption of orally administered, undigested, unchanged, and fully active peptide drugs. [9] This is in addition to delaying or targeting dosage forms. Since there are few peptidases in the large intestine, such unique delivery systems will have a good chance of getting their drug sufficiently absorbed after oral administration. [10] Obtaining slower release rates or longer release periods by applying thicker layers of conventional enteric coatings or extremely slow-releasing matrices is the simplest method for targeting drugs in the colon. [11]The many pharmaceutical techniques that can be used to create colon-targeted drug delivery systems are compiled in Table 1.

The efficiency of a colon-specific drug delivery system (CDDS) depends on the physical and chemical characteristics of the medication, the kind of delivery device, all other variables that may affect GI transit time, and the level of drug-GI tract interaction (1). To prevent the medication from being released in the stomach and small intestine, oral CDDS is crucial (4). As a result, some procedures used in the development of a CDDS have shown to be more effective than others in postponing the drug release until the system reaches the colon. Several commercial formulas claim to combine the traditional and more modern methods mentioned above (Table 2).

Table 1 Colon-targeted drug delivery systems

Target sites	Disease conditions	Drug and active agents
Topical action	Inflammation Bowel Diseases, Irritable bowel disease, and Crohn's disease. Chronic pancreatitis	Hydrocortisone, Budesonide Prednisolone, Sulfasalazine, Olsalazine, Mesalamine, Balsalazide,
Local action	Pancreatectomy and cystic fibrosis, Colorectal cancer	Digestive enzyme supplements 5-Fluorouracil
Systemic action	To prevent gastric irritation To prevent first-pass metabolism of orally ingested drugs Oral delivery of peptides Oral delivery of vaccines	NSAIDS Steroid Insulin typhoid

The delivery of these drugs specifically to the colon without being absorbed first in the upper gastrointestinal (GI) tract allows for a higher concentration of the drug to reach the colon with minimal systemic absorption. [12] The colonic contents have a longer retention time (up to 5 days), and the colonic mucosa is known to facilitate the absorption of several drugs, making this organ an ideal site for drug delivery. A drug can be delivered to the colon via the oral, or the rectal route. Oral dosage forms are the most preferred delivery route for colon-specific delivery due to their convenience. [13] Oral dosage forms also allow for a greater degree of flexibility in their manufacturing, design, improved patient adherence, and relatively safe administration, and they do not require sterile preparation. Direct rectal delivery of drugs is challenging concerning targeting a drug to specific sites within the colon. Additionally, the extent of drug distribution varies for different rectal dosage forms depending on their spreading capacity and retention time. The delivery of these drugs specifically to the colon without being absorbed first in the upper gastrointestinal (GI) tract allows for a higher concentration of the drug to reach the colon with minimal systemic absorption. The colonic contents have a longer retention time (up to 5 days), and the colonic mucosa is known to facilitate the absorption of several drugs, making this organ an ideal site for drug delivery. A drug can be delivered to the colon via the oral, or the rectal route. Oral dosage forms are the most preferred delivery route for colon-specific delivery due to their convenience. Oral dosage forms also allow for a greater degree of flexibility in their manufacturing, design, improved patient adherence, and relatively safe administration, and they do not require sterile preparation. Direct rectal delivery of drugs is challenging concerning targeting a drug to specific sites within the colon. Additionally, the extent of drug distribution varies for different rectal dosage forms depending on their spreading capacity and retention time.

2. The benefits of CDDS over traditional drug delivery

Nanotechnology, or molecularly produced systems and technologies, is a multidisciplinary scientific discipline that is rapidly expanding. The design of nanoscaled drug delivery systems is a subfield of this area.[14] Traditional medications, recombinant proteins, vaccinations, and more recently nucleotides may all be delivered with the help of nanoparticles. A related drug's kinetics, body distribution, and drug release are altered by nanoparticles and other colloidal drug delivery technologies. Other impacts include medication delivery that targets specific tissues or cells and the management of adverse effects. Thus, nanoparticles in the pharmaceutical biotechnology industry increase the therapeutic index and offer answers for upcoming delivery issues for new classes of so-called tech pharmaceuticals like recombinant proteins and oligonucleotides. [15]

Conventional drug delivery systems (DDS) have little control over how the medications are distributed and hardly any control over how to successfully concentrate on the target. Unpredictable and ever-changing plasma concentrations will be the result of this dosing method. Several commonly prescribed oral medications, including capsules and tablets, are made to release the active ingredient immediately after oral administration to ensure rapid and complete systemic drug absorption. 1) Short-term prescriptions require routine administration, increasing the chance of drug deliveries being missed due to poor patient adherence, which is one disadvantage of these traditional delivery modalities. 2) Typical plasma peak concentration. It is impossible to achieve a constant state because of how time is obtained. 3) Unavoidable changes in concentrationAs the values of CSS fall or climb above the therapeutic range, drug usage or presence is possible[16]. Oral medications that are swiftly absorbed in the food pipe and quickly eliminated from the blood are typically film-coated or given longer microencapsulation to extend their duration of action. However, the majority of these types have certain physiological drawbacks, such as gastrointestinal (GI) transit times, partial drug releases from devices, or prolonged prescription occupancy in the small intestine upper location resulting in low bioprotein-dosage forms of the long-term release.

2.1. Pharmaceutical methods for administering drugs specifically to the colon (CDDS)

2.1.1. Pharmacological delivery using a pH-sensitive polymer coating

The foundation of this strategy is the drug's pH-dependent release from the body. In this instance, it is used to transport medications to the colon efficiently by taking advantage of the pH difference between the upper and terminal regions of the GI tract. Remember that a variety of variables, including nutrition, food intake, intestinal motility, illness conditions, and intestinal pH, affect the intestine's and colon's pH. This makes it more difficult for the experts in this sector to build a delivery method that would be able to tolerate the variation in gastric pH as it passes from the stomach to the small intestine.Delivery systems have been created to deliver the medicine to the target place by integrating information on polymers and their solubility at various pH environments [14]. Colonic drug delivery methods utilizing frequently used copolymers of methacrylic acid and methyl methacrylate have been thoroughly studied. Following an in vitro comparison of Ethylenediamine® S and Eudragit® FS, it was determined that the latter would be better suitable for medication delivery to the ileocolonic area. [15]

Table 2 Enteric polymers used in the development of Modified Release Formulations for CDDS

Enteric polymer	Optimum pH for dissolution
Polyvinyl acetate phthalate (PVAP)	5.0
Methacrylic acid copolymer, Type A	>6.0
Eudragist FS30D	>7.0
Hydroxypropylmethylcellulose phthalate (HPMCP)	>5.5
Cellulose acetate time;state (CAT)	5.5
Hydroxypropylmethylcellulose acetate succinate (HPMCAS)	>6.0
Shellac (Marcoat 125 & 125N)	7.0
Methacrylic acid copolymer, Type B	>7.0

In reaction to a change in the solution's pH, pH-responsive polymers are prone to changing their structural makeup and physical characteristics such as surface activity, chain arrangement, and solubility. Therefore, when a pH-responsive

polymeric system comes into contact with a stimulating systemic pH, several types of events, such as shrinkage, swelling, gelling, or coating, occur. Because of their distinct properties, pH-responsive polymers are well suited for use in medication delivery, especially for targeted and controlled distribution.Electrolyte concentration, transit duration, and inter- and intra-subject variability are some of the major factors affecting performance along this pathway. Despite these drawbacks, pH-based systems are commercially available for the treatment of ulcerative colitis and Crohn's disease, respectively, for mesalazine (5 ASA) (Asacol® and Salofalk®) and budesonide (Budenofalk® and Entrocort®).

2.2. Time-controlled release system (TCRS)

Sustained or delayed-release dosage forms are examples of time-controlled release systems (TCRS), which hold great promise for medication delivery. However, in these techniques, the colon arrival time of dosage forms cannot be properly anticipated, leading to low colonial availability because of the possibly significant variability in the stomach emptying time of dosage forms in humans. 26 By extending the lag period by about 5 to 6 hours, the dosage forms may also be used as colon-targeting dosage forms. However, this method has the following drawbacks:

- The rate at which the stomach empties varies greatly across individuals or is influenced by the kind and quantity of food consumed.
- Changes in the gastrointestinal transit of the medicine would be caused by gastrointestinal movement, particularly peristalsis or contraction of the stomach.
- IBD, carcinoid syndrome, diarrhea, and ulcerative colitis patients have been seen to move more quickly through various parts of the colon. [16-17]

As a result, time-dependent methods are not the best for delivering medications to the colon specifically for the treatment of disorders associated with the colon. It may be possible to enhance the site specificity of medication administration to the colon by properly integrating pH-sensitive and time-release characteristics into a single dosage form.

A pulsatile medication delivery system is another name for it. Pulsatile release systems are designed to release loaded medications rapidly and completely after a lag time of a specified amount of time without release (s). The strategy is based on the idea that drug release should be postponed until the colon has been reached in the digestive system. Since small intestine transit takes about 3–4 hours and is generally consistent and not greatly impacted by the type of formulation taken, a lag time of 5 hours is typically regarded as adequate. This technique has many benefits over traditional oral drug delivery methods, including improved patient compliance, decreased dosage and frequency, fewer side effects, a practically constant drug level at the target site, and the avoidance of peak and valley fluctuations.[18]

2.2.1. Pressure-dependent delivery

The pressure-controlled colon delivery capsule makes use of the colon's luminal contents' increased pressure. The reabsorption of water in this area is what causes the rise in luminal pressure. For the manufacture of such a system, the medicine is mixed with the suppository base and coated with ethyl cellulose. The body's temperature causes the suppository base to melt and increases the volume, creating a balloon-like structure of ethyl cellulose that is filled with liquid. This balloon can survive minor bowel contractions (peristalsis), but it bursts when the colon contracts vigorously and has thicker viscosity. This technique is employed to produce systems that consist of just one unit[19].

2.2.2. Bacteria-dependent delivery

Colonic microorganisms are used in this technique to break down the substrate. The colon is thought to contain roughly 400 types of bacteria, with an estimated quantity of 1011 bacteria per gram (anaerobic in nature). In the past, polymer cross-linked with azo aromatic groups was used, but nowadays, natural polysaccharides are used due to their potential carcinogenic activity. Natural polysaccharides typically release drugs too early, so they must be chemically altered or combined with hydrophobic polymers. While this polymer exhibits good film-forming abilities and is resistant to pancreatic enzymes, it will degrade when exposed to bacterial enzymes.[20]

3. Methodology

The Colon Site-Specific Drug Delivery (CDDS) For site-specific medication delivery, various strategies are employed. Among the main strategies for CDDS are these:

3.1. pH-Sensitive Polymer Coated Drug Delivery

TheCoating During a fast, the stomach's pH is between 1 and 2, but after eating, it rises. The proximal small intestine has a pH of around 6.5 and the distal small intestine has a pH of around 7.5. There is a considerable pH drop from the ileum to the colon. In the cecum, it is around 6.4. However, in the ascending colon of healthy volunteers, pH levels as low as 5.7 have been seen. 20 The pH in the descending colon is 7.0, while it is 6.6 in the transverse colon. These variations in pH levels form the basis for the use of pH-dependent polymers. The polymers identified as pH-dependent in the delivery of colon-specific drugs are insoluble at low pH levels but become more soluble asRises in pH.Although a pH-dependent polymer can shield a formulation in the stomach and proximal small intestine, the formulation's site-specificity may be subpar and it may start to dissolve there.Long lag durations at the ileocecal junction or quick transit through the ascending colon can also be problems caused by the pH fall from the end of the small intestine to the colon, which can similarly hurt the site-specificity of enteric-coated single-unit formulations.

3.2. Delayed (Time Controlled Release System) Release Drug Delivery to Colon

A very promising method of medication release is the time-controlled release system (TCRS), which includes dose forms with delayed or sustained release. However, these approaches cannot accurately predict the colon arrival time of dosage forms because of the potentially significant variations in gastric emptying times of dosage forms in humans, leading to poor clinical availability. 23 By extending the lag time by about 5 to 6 hours, the dosage forms might also be used as colon-targeting dosage forms.

3.3. Microbially Triggered Drug Delivery to Colon

The colon's microflora is composed primarily of anaerobic bacteria, such as Bacteroides, bifidobacteria, eubacteria, clostridia, enterococci, enterobacteria, and echinococcus, and is in the range of 1011 -1012 CFU/mL. 25 Various substrates, such as di- and tri-saccharides, polysaccharides, etc., that have been left undigested in the small intestine are fermented by this massive microflora to meet its energy requirements. 29,30 Numerous enzymes, including glucuronidase, xylosidase, arabinoside, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase, are produced by the microflora for this fermentation. 31 Because biodegradable enzymes are exclusively present in the colon, using biodegradable polymers for colon-specific medication delivery appears to be a more site-specific strategy than other strategies. 5 These polymers protect the medication from the surroundings of the small intestine and stomachand can transport the medication to the colon. They are broken down by enzymes, microorganisms, or the polymer's backbone once they reach the colon, which causes their molecular weight to drop and their mechanical strength to decrease. 32-36 The drug entity escapes from its grasp at that point.

4. Newly Developed Approaches for CDDS

4.1. Pressure Controlled Drug-Delivery Systems-

The colon experiences greater pressure than the small intestine. Itcreated water-insoluble ethylcellulose-based pressure-controlled colon-delivery capsules.In such systems, drug release occurs following the disintegration of a water-insoluble polymer capsule because of pressure in the lumen of the colon. The thickness of the ethylcellulose membrane is the most important factor for the disintegration of the formulation.The mechanism also seems to be influenced by capsule density and size. The colon's luminal material has a higher viscosity than the small intestine's due to the colon's reabsorption of water. Therefore, it has been determined that oral drug delivery to the colon may be complicated by drug dissolution in the colon.The medication is in a liquid form in pressure-controlled ethylcellulose single-unit capsules. When pressure-controlled capsules were given to humans, three to five-hour lag durations were seen between the drug absorption and the administration of the medication.

4.2. Novel Colon Targeted Delivery System (CODESTM)

To circumvent the inherent issues with pH- or time-dependent systems, CODESTM is a novel CDDS technology. A combination method of pH-dependent and microbial-triggered CDDS is known as CODESTM. It was created using an original mechanism incorporating lactulose, which catalyzes site-specific drug release in the colon. The system comprises a conventional tablet core made of lactulose that is then covered in an acid-soluble material called Eudragit E and an enteric material called Eudragit L. The idea behind the technique is that the enteric coating, which shields the pill while it's in the stomach, will swiftly dissolve after gastric emptying. The coating made of acid-soluble substance then safeguards thegut, tiny. When the tablet enters the colon, the bacteria break down the polysaccharide (lactulose) into organic acid using enzymes. This causes a sufficient drop in pH around the system to cause the coating's disintegration and subsequent medication release.

5. Conclusion

An important site for the transport and absorption of drugs is the colonic region of the GIT. In terms of both local and systemic treatment, CDDS gives patients several therapeutic advantages. Colonic bacterial enzymes that break down natural materials are more likely to be used in systems that aim to attain colon specificity. The development and validation of a dissolution method that incorporates the physiological features of the colon while still being able to be used frequently in an industrial setting for the evaluation of CDDS present challenges for pharmaceutical scientists given the sophistication of colon-specific drug delivery systems and the uncertainty of current dissolution methods in establishing potential in-vitro/in vivo correlation.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no potential conflict of interest.

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