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Colon Target Drug Delivery System Review

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Abstract: *For the local treatment of a number of bowel disorders such as ulcerative colitis, Crohn's disease, amoebiasis and sand, colonic cancer, the local treatment of colonic pathologies, and the systemic distribution of protein and peptide medicines, targeted drug delivery into the colon is extremely desirable. A medication must be properly formulated for colon-focused drug delivery. To ensure sudden or controlled release in the proximal colon, the substance must first be shielded from degradation, release, and absorption in the upper GI tract. The advantages and disadvantages, cutting-edge methods for colon-targeted drug delivery, clinical evaluation methods, and some details about commercial dosage forms are the main topics of this paper..*

Keywords: Colonic drug delivery system, Drug targeting, Drug targeting, Novel approaches, gamma scintigraphy

I. INTRODUCTION

Targeted medication administration into the lower GI tract via the colon, primarily in the large intestine, is referred to as colon delivery (i.e. Colon). (1) For the localised treatment of numerous colonic disorders, particularly inflammatory bowel disease (Crohn's disease and ulcerative colitis), the site-specific administration of medications to lower sections of the GIT is favourable.

colon cancer as well as irritable bowel syndrome. Because the digestive system's enzymes are less diverse and intense in the colon, and because colon mucosal proteolytic activity is much lower than that found in the small intestine, CTDDS prevents peptide drugs from being hydrolysed and degraded by enzymatic means in the duodenum and jejunum before releasing them into the bloodstream.

medication into the colon or ileum, increasing its systemic bioavailability. In the last 25 years, oral

controlled release formulations for the small intestine and colon have drawn a lot of attention due to a number of factors, including pharmacological superiority and therapeutic advantages associated with the drug release pattern that is not possible with conventional products with the rapid or prolonged release.

(2). Additionally, the importance of colon drug delivery has grown. It is now a potential site for the systemic administration of therapeutic proteins and peptides that are administered intravenously in addition to the systemic administration of medications for the treatment of local diseases. When taken orally, these delivery systems enable medications to be released from the delivery system once they reach the colon. (3,

Need of Colon Targeted Drug Delivery

Drug administration into the colon specifically helps cure disorders there since there are fewer systemic side effects and the dosage can be reduced.

Colon-specific formulation is helpful for administering proteins and peptide medications, as well as to extendmedication administration.

Drugs that are polar or sensitive to chemical and enzymatic breakdown in the upper GI tract, which is greatly impacted by hepatic metabolism, can be delivered using colon targeted drug delivery.

If medications are specifically prescribed for the colon, serious colon disorders can be treated more successfully.

The colon is divided into 5 primary segments, each measuring around 5 feet (150 cm) in length. The stomach, small intestine, and large intestine make up the GI tract. There are three main sections of the large intestine, which extends from the ileocecal junction to the anus. In Figure 1, The three are the rectum, colon, and anal canal. Folds during

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pregnancy are known as mesentery, which the ascending and descending colon support. The cecum, ascending colon, and hepatic flexure make up the right colon. The descending colon, splenic flexure, and sigmoid make up the left colon. Before the anus, the rectum is the last anatomical component. The villi, lymph, muscle, nerves, and arteries are all found in the tissue of the colon. Each device has a large absorptive capacity, holding around 2000ml of fluid.

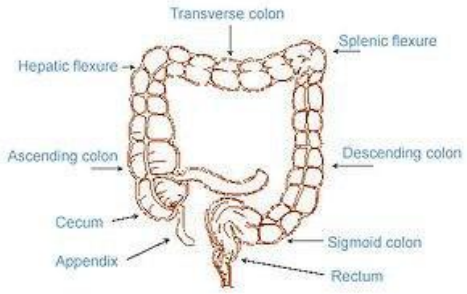

Fig 1: Colon and it's segment

Advantage

The site-specific administration of medications to the lower GI tract is useful for the localised treatment of a number of colonic disorders, especially inflammatory bowel disease, irritable bowel syndrome, and colon cancer.

- Used in direct treatment of disease at that site, low dosing and fewer systemic side effects.
- Useful for the delivery of proteins, peptides that are being delivered by injections.
- Delayed mechanisms are designed to improve the efficacy of the drug by concentrating the drug molecules where they are needed most.
- Peptides and proteins may be better absorbed from the lower GIT than those molecules that are poorly absorbed in the upper gut.
- Both of these occur in the colon.

Disadvantages

- Drugs with greater plasma levels and hence increased bioavailability in general, but notably for those that are substrates for this kind of enzyme, benefit from a prolonged residence period of 3-5 days.
- One drawback of single-unit targeted medication delivery systems is the unintentional breakdown of the colon. due to an insufficient production process or unique stomach physiology
- Due to several biological hurdles, developing drugs for the colon is challenging.
- The intestinal mucosa has a decreased affinity for drug metabolising enzymes of the cytochrome (P450) class. (8,10)

Limitation

The colon offers a near neutral pH, reduced enzyme activity, a long transit time, and greater responsiveness to absorption enhancers at the site of medication delivery.

- The gastro intestinal tract contains a wide variety of pH values and several enzymes that
- Before entering the colon, the dosage form should be in solution form for better drug delivery because the colon has a lower fluid content and a more viscous environment than the upper part of the GI tract. Drug stability is also a concern and must be taken into account when designing the delivery system.
- The medication could perhaps attach in an unspecific manner to food residues, intestinal fluids, mucus, or faecal debris.

Factors Governing the Colon Drug Delivery

Colon medication delivery influencing factors can be broadly classified into two categories:

1. Physiological factors
2. Pharmaceutical factors

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Physiological Factors

Gastrointestinal Transit

In a fasting state, the digestive tract goes through 4 phases over the course of 2 to 3 hours. The uneven contractile activity during the eating state alters the typical pattern.

Transit of the Small Intestine

The physical state, the size of the dosage form, or the presence of food in the stomach have little effect on small intestinal transit. The dose form typically takes 3–4 hours to go to the ileocecal junction and the passage of time is constant.

Colon Transit

The colonic transit time has the potential to have a significant impact on the bioavailability of medications released from dosage forms. The size of the dose form, the gender of the patient, and physiological factors including stress, food intake, disease, and the presence of food all affect the colonic transit time. Solutions and small particles move slowly through theMen exhibit a shorter colonic transit time than women in the proximal colon and in humans. Adults' colonic transit times for capsules range from 20 to 35 hours, and they are unaffected by the density or volume of the capsule

Stomach Emptying

Fastest and most reliable gastric emptying. Depending on the state of the stomach at the time of drug administration, emptying can take anywhere from 5 to 10 minutes to 2 hours. The fes condition can significantly slow down gastric emptying.

Stomach and Intestinal pH

The gastrointestinal pH affects the release and absorption of medicines taken orally. (Table-1)

Sr.No	Organ	Ph
1	Stomach	1.5(fasted state)2-6 (fed state)
2	Small intestine	6.6-7.5
3	Right colon	6.4
4	Mid colon	6.6
5	Left colon	7

Colonic Microflora and Enzymes

Both the mouth cavity and the colon/rectum, which are the endpoints of the human alimentary canal, are densely populated with bacteria and other microflora. The colonic microflora's azoreductase, which catalyses the release of 5-amino salicylic acid from a variety of delivery methods, plays a significant role in their growth.

different prodrugs. Other enzymes include glycosidase and glucuronidases, which are made by bacteroid, bifidobacterial, and lactobacilli. The concentration of bacteria in a given area is related to the enzyme's activity.

Colonic Absorption

Because the colon has a significantly less surface area than the small intestine, it is not the best place for absorption. The colon is a potential drug delivery site since it contains endogenous enzymes that are not of microbial origin. Colon is present for 10 to 24 hours. A little blending in the colon allows the creation

Of surroundings close by with the best absorption. Water, electrolytes, and ammonia are transported across the mucosa and have a greater impact on absorption in the proximal colon and distal colon.

Absorption Mechanisms

the movement of colonocytes (transcellular transport)

Interacting with adjacent colonocytes (paracellular transport)Absorption enhancers encourage effective absorption through a variety of ways. By denaturing membrane proteins, changing lipid-protein interactions, upsetting lipid

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integrity, and damaging the intracellular occluding junction complex, which opens the paracellular route, they are changing epithelial permeability.

Absorption of Colonic Macromolecules

The colon can absorb 0.13% of bovine serum albumin while the small intestine can absorb 1.7% of it. Because the surface areas are different, oocytes.

Condition of Gastrointestinal Disease

Gastrointestinal illnesses like Crohn's disease, diarrhoea, constipation, and gastroenteritis can alter the release and absorption properties of colon-specific drug delivery systems.

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Drug Traffickers

The selection of a carrier for a particular drug candidate is influenced by the physicochemical composition of the medicine as well as the disease that the system is meant to treat. The choice of carrier is influenced by the drug's chemical composition, stability, partition coefficient, and kind of selected absorption enhancer. (7,11,12)

Targeted Strategies for Colon

Colon-specific drug administration is regarded to be advantageous for oral protein and peptide medicine delivery as well as the treatment of illnesses related to the colon. The following are some methods for administering medication specifically to the colon:

1. Coating with a ph-dependent polymer
2. Osmotic control system
3. Pressure delivery systems
4. Coating made of biodegradable polymer without regard to ph
5. Delivery strategies based on the metabolic processes of gut bacteria
6. A pulsing medicine delivery system
7. Time-controlled or time-dependent system

Making Coatings using PH-Dependent Biodegradable Polymers: -

The coatings on capsules are constructed of biodegradable azo polymers with excellent degradation properties and great hydrophilicity. The medication may escape the body before it reaches the colon when hydrophilicity is higher. For azo polymer systems, the delivery of peptides, hormones, and other drugs with a constrained therapeutic window is inappropriate.

Nonetheless, they are suitable for administering local medications to the colon. The most often used polymers are the methacrylic acid co-polymers Eudragit L and Eudragit S. The carboxyl polymer dissolves as salts at pH 5.5 and disperses in water to form latex, eliminating the need for organic solvents in the coating operations.

The operation of biodegradable azo polymer systems is shown in Figure 2.

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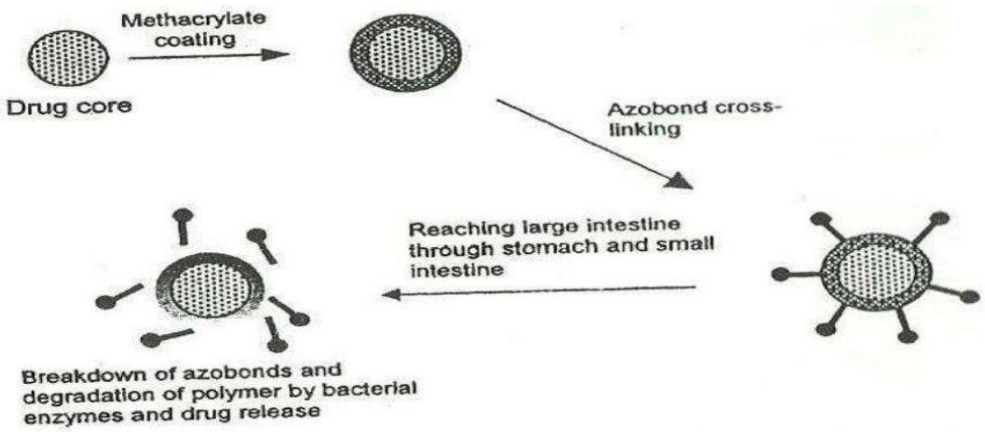

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Figure 2: Working principle of the biodegradable azo polymer system

A single osmotic unit or up to five or six push-pull units, each measuring 4 millimetres in diameter and housed inside a hard gelatin capsule, can make up the ORDS-CT (Alz Company) system. Each bilayer push-pull unit contains an osmotic push layer and a drug layer, both of which are enclosed by a semipermeable membrane (Fig.3). When the unit enters the small intestine, the covering melts in this higher pH environment compartment.

Mechanisms

The intestinal contents grind and protrude due to the pressure produced by the muscle contractions of the gut wall. This pressure causes the medication to come out of the capsule shell.

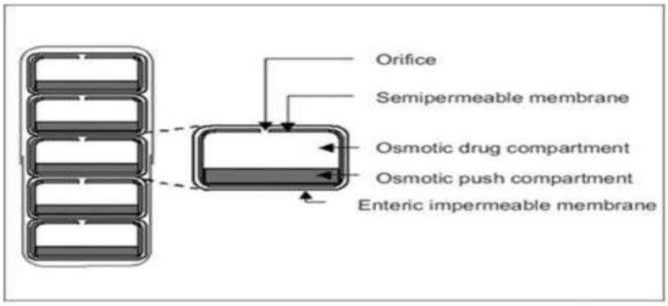

fig 3: Cross section of the OROS-CT colon targeted drug delivery system

Controlled Pressure System

Designing a pressure control system is based on the luminal pressure of the colon. The unique delivery system uses a capsule that can sustain pressure in the upper GIT but bursts in the big intestine due to the increasing pressure. The digestive processes in the GI tract involve contractile action of the

Peristalsis and stomach motions drive the contents of the intestinal tract. These strong peristaltic waves in the colon occur 3–4 times per day and are only momentary in duration. The capsule walls' thickness, which in turn determines how soon the capsules collapse in the large intestine, may be precisely controlled thanks to the ethyl cellulose employed in their production.

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Biodegradable Polymer Coating with Ph-Independence

Drugs coated with polymers that break down owing to the action of colonic bacteria can be used in the design of pharmaceuticals for colon targeting to release an orally given medicament in the colon.

Delivery of Drug Based on Microflora's Metabolic Activity

Prodrugs

A generic chemical approach is widely used in prodrug design to mask unfavourable drug properties such low bioavailability, poor site specificity, and chemical instability. Prodrugs with the potential to act as a drug delivery system include those that target a specific membrane transporter, an enzyme, or both, especially for colon cancer chemotherapy.

For instance, ulcerative colitis and Crohn's disease are both treated with sulphasalazine.

Hydrogels

Hydrogels contain both enzymatically degradable azo aromatic cross connections and acidic co-monomers. Many drug delivery devices have been proposed to convey the medication for efficient therapy. It is widely known that the polymeric matrix enables the controlled release of antimicrobial agents.

Oxytetracycline, amoxicillin, metronidazole, and tetracycline HCL are a few examples.

Pulsating drug administration:

Immediately following a precisely defined lag time, the medication is released in pulsed drug administration. The main elements that control the interval before rupture are permeation, the mechanical properties of the polymer coating, and the swelling behaviour of the swelling layer.

Methods for pulsatile drug delivery systems include the capsular system, the osmotic system, solubilization or erosion of the membrane, and membrane rupture.

Systems that control or depend on time:

A time-dependent approach is effective for synchronising drug administration. Regardless of the formulation type, the small intestine transit time is constant (Fig 4). Using mechanisms that are safeguarded in the stomach and formulations that target drug release on the colon can reduce variation in gastric resident time.

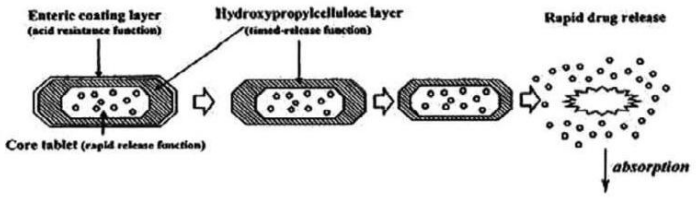

FIG 4: Design Of Enteric Coated Timed-Release Press Coated Tablet(ETP Tablet).

Assessment Tests

To evaluate the ability of various carrier systems to transport drugs precisely to the colon, numerous in-vitro procedures are used.

Tests for in vitro dissolution

Drug carriers' capacity to hold up in the stomach and small intestine is commonly assessed using drug release experiments conducted in 0.1NHCl for 2 hours. The conventional method of dissolution in various buffers is useful to ascertain whether an enteric coating can prevent medicine release in the stomach and small intestine. Dissolution

Studies on colon-specific medicine delivery systems may be carried out using the conventional basket method.

The medium, for instance, had a jejunal area pH of 6.8 and an ileal segment pH of 7.2 to encourage stomach juice.Tests for in vivo evaluation

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Rats, dogs, guinea pigs, and pigs are widely employed to examine the transit of drugs to the colon due to their similar anatomical and physiological properties. Thyme naked mice carry the human foetal gut into a subcutaneous network that develops, vascularizes, and can create mucosal immune

Clinical Assessment Exams:

A colonoscopy and intubation can be used to study the absorption of drugs from the colon. The two techniques that are most frequently used now to evaluate colon medicine delivery systems are gamma-scintigraphy and high-frequency capsules.

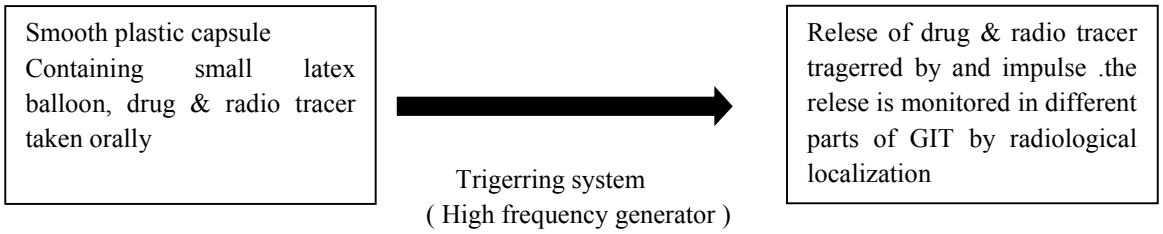
Gamma-Scan Imaging:

A colonoscopy and intubation can be used to study the absorption of drugs from the colon. The two techniques that are most frequently used now to evaluate colon medicine delivery systems are gamma-scintigraphy and high-frequency capsules.

Technique of High Frequency Capsules:

High Frequency Capsules Method

This technique is used to assess the drug's capacity for intestinal absorption. The relative bioavailability of intestinal medicine administration strategies can be evaluated using high frequency capsules. Advantages are relative in this case. To compare various absorption parameters, drug release at various GIT sites within the same item can be used. Any GIT site's bioavailability can also be evaluated.



Technique Employed In Marketed Drug.

Technique Employed	Polymers used	Drug used	Reference
Ph dependent	Eudragit L 100&S100	mesalazine	20
	Eudragit S,30dFS,eudragit P4135F	predniosolone	21
	Eudragit L,30D55,eudragit FS 30D	paracetemol	22
Time dependent	Hydroxyethyl cellulose	theophylline	23
Time dependent	Hydroxethyl propyl methyl celleulose	Psedophedrine HCL	24

Formulation and Doses of Marketed Drug

DRUG	TRADE NAME	FORMULATION	DOSE	REFERENCE
1.mesalime	Asacol	Eudragit ‘s’coated tablet	0.8-2.4/day	53
2.mesalime	Salotac	Eudragit ‘s’coated tablet	1-4g/daySS	53
3.mesalime	Pentaza	Controll relese EC coated tablet	1.5-4g/day	53
4.mesalime	Claversal	Eudragit ‘L’coated tablet	1-2g/day	53
5.mesalime	Entort	Eudragit ‘L’coated tablet	9mg/day	53
6.mesallime	dipentum	5-ASA dimer as capsule	1g/day	53

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II. CONCLUSION

Because it uses a smaller amount of the drug, is only administered when necessary, and keeps the medication as close to the target region as possible in its intact form, drug delivery to the diseased colon is favourable. Colonic administration might be enhanced by safeguarding the medication against environmental factors or absorption.
the proximal colon, which is where colonic targeted drug administration from the upper GIT takes place.
All of the approaches provide strategies to address local conditions involving the colon or to improve the body's absorption of poorly absorbed drugs. The widespread bacteria in the colon can be exploited to target the drug release there.

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