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A Comprehensive Review Oncolon Targeted Drug Delivery System

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ABSTRACT
Local therapy of bowel disorders like ulcerative colitis, Crohn's disease, amoebiosis, colonic cancer, local treatment of colonic pathologies, and systemic distribution of protein and peptide medications all benefit from targeted drug delivery into the colon.A drug must be shielded from degradation, release, and absorption in the upper Gastrointestinal tract before being released abruptly or regulated in the proximal colon to enable successful colon focused drug delivery.The advantages and disadvantages, emerging methods in colon targeted drug administration, clinical evaluation procedures, and some information on licenced dose forms are all covered in this paper.
Keywords Colon Targeted Drug Delivery System, Biodegradable Polymers, Osmotic Controlled System

I. INTRODUCTION

Targeted drug administration into the lower GI tract, especially the large intestine, is known as colon delivery (i.e. Colon).The localised therapy of numerous colonic disorders, primarily inflammatory bowel disease (crohn's disease and ulcerative colitis), irritable bowel syndrome, and colon cancer, benefits from site-specific drug administration to lower portions of the GIT.For the following reasons, the colon is thought to be a good absorption location for peptides and protein drugs:CTDDS protects peptide medicines from hydrolysis and enzymatic degradation in the duodenum and jejunum, and then releases the medication into the ileum or colon, resulting in increased systemic bioavailability.In the last 25 years, oral controlled release formulations for the small intestine and colon have gotten a lot of attention for a number of reasons, including pharmaceutical superiority and clinical benefits resulting from the drug release pattern that aren't possible with traditional immediate or extended - release products.Colon drug delivery has become increasingly essential, not only for the systemic dispersion of drugs for the treatment of local illnesses, but also as a potential site for the systemic delivery of therapeutic proteins and peptides delivered through injection.When administered orally, these delivery systems allow medications to be released from the delivery system once they reach the colon.

Need of Colon Targeted Drug Delivery

- Metabolic activities such as azo reduction and enzymatic cleavage take place in the colon, and are responsible for the synthesis of many medications and peptides like insulin.Drugs can be delivered both locally and systemically through the colon. Topical therapy of inflammatory bowel disease is possible with local administration.
- The colon has a highwater absorption capacity, but the colonic contents are viscous, making most medications unavailable to the absorptive membrane.
- Metabolic activities such as enzymatic cleavage and azo reduction and take place in the colon, and these are responsible for the synthesis of many medications and peptides like insulin.

DISADVANTAGES

- Medicines with a longer residence period of 3-5 days have greater plasma levels and thus increased bioavailability in general, but notably for drugs that are substrates for this category of enzyme.
- The unintended breakdown of the formulation due to manufacturing deficiencies or atypical gastric physiology is a drawback of the single unit colon focused drug delivery method.
- Many biological hurdles make developing a colon-specific medication difficult.
- The intestinal mucosa has a decreased affinity for the cytochrome (P450) class of drug metabolising enzymes.

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LIMITATIONS

- At the site of drug delivery, the colon provides a near neutral pH, reduced enzyme activity, a long transit time, and improved responsiveness to absorption enhancers.
- The gastro intestinal system contains a wide range of pH levels and enzymes through which the dose form must pass before reaching the target site.
- It should be in solution state before entering the colon for optimum drug delivery.
- The colon has a lower fluid level and is more viscous than the rest of the GI tract.
- Drug stability is another factor that must be considered while building the delivery system. Dietary residues, digestive fluids, mucus, and faeces may all attach to the medication in an unspecific fashion.
- The local microbiota may influence colonic performance by affecting medication metabolism.
- Drug bioavailability is also affected by lower surface area and relative tightness.

FACTORS GOVERNING THE COLON DRUG DELIVERY

Factors which influence colon drug delivery are mainly divided into 2 types;

- Physiological factors.
- Pharmaceutical factors.

Physiological Factors

Gastrointestinal Transit

Fasted gastrointestinal motility goes through four phases over the course of 2-3 hours. By causing erratic contractile activity, the eating state alters the typical pattern.

Transit of Small Intestines

Small intestinal transit is unaffected by physical condition, dosage form size, or the existence of food in the stomach.The dose form's average transit time to the ileocecal junction is about 3-4 hours, and this time period is consistent.

Colonic Transit

The colonic transit time has a significant impact on the bioavailability of medicines released from dosage forms.The colonic transit time is affected by a number of parameters, including gender and dosage form size, as well as physiological situations such as stress, food intake, and illness state.Small particles and solutions travel through the proximal colon slowly, and men have a faster colonic transit time than women.Humans have a 20-35-hour capsule transit time in the colon, which is unchanged by capsule density or volume.

Gastric Emptying

Gastric emptying is the quickest and most reliable method.Depending on the phase of the stomach at the time of drug administration, emptying can take anywhere from 5-10 minutes to 2 hours.The fed condition can significantly impede gastric emptying.

Stomach and Intestinal pH

The pH of the gastro intestinal tract affects the release and absorption of medications taken orally. (Table-1)

Table -1: pH of GIT at various sites

Sr.no	Organ	pH
1	Stomach	1.5-2 (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 ends of the human alimentary canal, the mouth cavity and the colon/rectum, are densely populated with bacteria and other microflora. The colonic microflora's azoreductase plays a key role in the development of a range of delivery systems, particularly in catalysing the release of 5-amino salicylic acid from a variety of prodrugs.Lactobacilli, bacteroids, and bifidobacteria generate glycosidase and glucuronidases, among other enzymes. The activity of an enzyme is related to the amount of bacteria present in a given area.

Colonic Absorption

Because the surface area of the colon is substantially smaller than that of the small

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intestine, it is not well adapted for absorption.Because the environment divides endogenous enzymes that are not of microbial origin, the colon is explored for drug administration.The colon's resident time is 10 to 24 hours.It is feasible to generate local habitats with maximum absorption with little mixing in the colon.The movement of water, electrolytes, and ammonia across the mucosa influences absorption, which is particularly so in the proximal and distal colons.

Mechanisms of Absorptions

- Passing through colonocytes (transcellular transport)
- Passing between adjacent colonocytes (paracellular transport)

Absorption enhancers work through a variety of techniques to aid efficient absorption.The paracellular pathway is opened by disruption of the intracellular occluding junction complex, modulation of epithelial permeability by denaturing membrane proteins, modification of lipid protein interactions, and breakdown of the integrity of the lipid barriers by colonic enterocytes.

Colonic Absorption of Macromolecules

Bovine serum albumin absorbs 0.13 percent from the colon and 1.7 percent through the small intestine. This is due to the variation in surface area.

Gastrointestinal Diseased State:

The release and absorption qualities of colon specific drug delivery systems may be affected by Crohn's disease, constipation, diarrhoea, and gastroenteritis.

Pharmaceutical Factors

Drug Molecules

Peptide medicines, which have poor absorption in the stomach or intestine, are best suited for colon specific drug delivery systems.Sulphasalazine and 5-ASA are common medications used to treat IBD and other disorders.

Drug Carriers

The choice of carrier for a given medication candidate is determined by the drug's physicochemical characteristics as well as the ailment for which the system will be utilised.The chemical makeup of the medicine, its stability and partition coefficient, and the type of absorption enhancer used all have an impact on carrier selection.

Targeting Approaches to Colon

Colon specific medication delivery is regarded to be beneficial in the treatment of colon problems and the oral delivery of protein and peptide medicines.The following mechanisms are used to deliver drugs to the colon:

1. Using pH-dependent polymers to coat
2. System of osmotic control
3. Pressure distribution systems
4. Biodegradable polymers that are pH independent.
5. Delivery techniques based on intestinal bacteria's metabolic activities.
6. Drug delivery system that pulses.
7. Time-dependent or time-controlled system.

Coating With PH Dependent Bio Degradable Polymers

Biodegradable azo polymers with high hydrophilicity are utilised to coat capsules and have outstanding degradation characteristics.Drugs with a higher degree of hydrophilicity may be released from the system before they reach the colon.Peptides, hormones, and other medications with a limited therapeutic index are not suited for distribution via azo polymer systems; nonetheless, they are suitable for local delivery of pharmaceuticals to the colon.Methacrylic acid co polymers, also known as eudragit L and eudragit S, are the most often utilised polymers. Carboxyl polymer forms salts at pH 5.5 and dissolves in water to create latex, eliminating the need for organic solvents in coating operations.The working concept ofbiodegradable azo polymer systems is shown in Figure 2.

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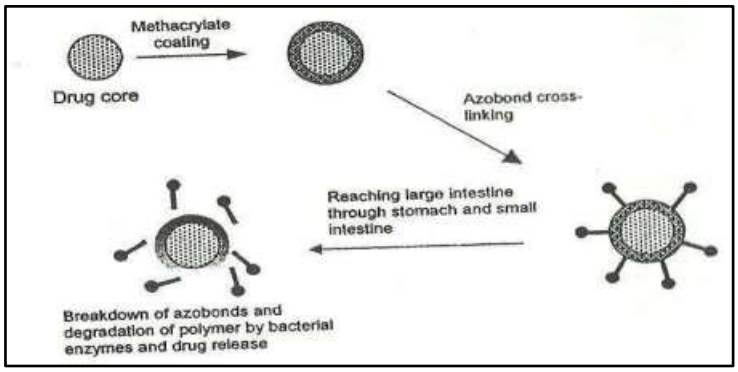

Figure-2: Working principle of biodegradable azo polymer systems.

Osmotic Controlled System (ORDS-CT)

The ORDS-CT (Alza Corporation) system can consist of a single osmotic unit or as many as 5-6 push-pull units, each measuring 4mm in diameter and enclosed in a hard gelatin capsule.An osmotic push layer and a drug layer are both enclosed by a semipermeable membrane in each bilayer push-pull unit (Fig.3).The covering dissolves as the unit enters the smallintestine, where the pH is greater.

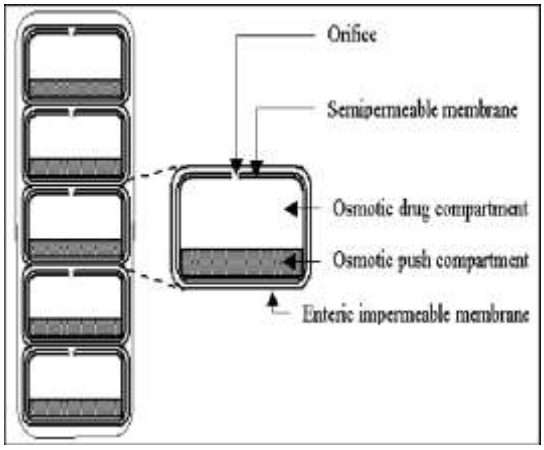

Fig.3: Cross Section of the OROS-CT colon targeted drug delivery system

Mechanism

The pressure created by the muscle contractions of the gut wall is responsible for the grinding and propulsion of the intestinal contents.The medication is released from the capsule shell due to this pressure.

Pressure Controlled System

The design of pressure control systems is based on the luminar pressure within the colon.The specific delivery is in the form of a capsule that can withstand upper GIT pressures but collapses in the large intestine due to elevated pressure. Contractile activity of the stomach and peristaltic motions for propulsion of intestinal contents are involved in the digestion processes within the GI tract.Strong peristaltic waves in the colon last only a few seconds and occur only 3-4 times per day.The capsule shells are constructed of ethyl cellulose, and the capsule shell wall thickness can be changed to control the capsule's breakdown time in the large intestine.

COATING WITH PH INDEPENDENT BIODEGRADABLE POLYMERS

Pharmaceuticals coated with polymers that degrade due to the action of colonic microbes can be used to create drugs for colon targeting, allowing an orally delivered agent to be released in the colon.

DELIVERY OF DRUGS BASED ON METABOLIC ACTIVITY OF MICROFLORA

Prodrugs

Prodrug design is frequently used to disguise undesirable drug qualities such as inadequate bioavailability, lack of site selectivity, and chemical instability. Prodrugs that target a specific enzymes or membrane transporter, or both, could be utilised to give chemotherapy to patients

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with colon cancer.Example- Treatment of ulcerative colitis and Crohn's disease with sulphasalazine.

Pulsating Drug Delivery

The medicine is released rapidly after a predetermined lag time in pulsing drug delivery.Permeation, mechanical properties of the polymer coating, and swelling behaviour of the swelling layer all influence the lag time before rupture.Capsular system, Osmotic system, solubilization or erosion of membrane, and membrane rupture are all methods for pulsatile drug delivery systems.

Time Control/Dependent Systems

A time-dependent approach is beneficial for synchronised medication administration.The duration of transit through the small intestine is unaffected by the kind of formulation (Fig 4).Medicine release can be targeted on the colon by using formulations that release drug after a specified time after gastric emptying.Coatings for tablets that release medicine from a core after a lag time have been made using a mix of hydrophilic (HPMC) and hydrophobic polymers.Water insoluble ethyl cellulose and a swellable polymer were also used to create time-controlled formulations.

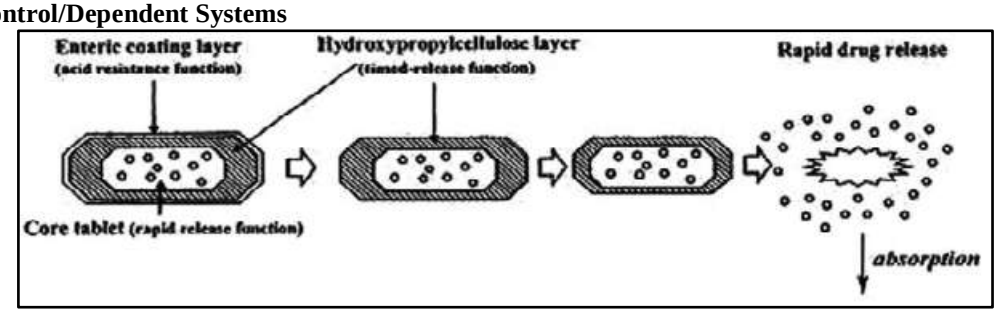

Fig 4: Design Of Enteric Coated Timed-Release Press Coated Tablet(ETP Tablet)

EVALUATION TESTS

Different in-vitro procedures are used to assess the potential of different carrier systems to deliver medications particularly to the colon.

Invitro Dissolution Tests

Drug release tests in 0.1NHCl for 2 hours are commonly used to assess the ability of coatings or carriers to remain intact throughout the stomach and small intestine.For evaluating the capacity of an enteric coating to limit drug release in the stomach and small intestine, the traditional approach of dissolution in various buffers is useful.The traditional basket method can be used to perform dissolution studies on drug delivery devices for the colon.For example, pH 1.2 stimulates stomach fluid, 6.8 stimulates the jejunal region, and 7.2 stimulates the ileal segment.

Invivo Evaluation Tests

Guineapigs, dogs, pigs, and rats are commonly used to test medication transport to the colon since their anatomical and physiological structures are similar.The human foetal bowel is implanted into a subcutaneous tissue on the back of thyme naked mice, which vascularizes in 4 weeks, develops, and is capable of forming a mucosal immune system.

Clinical Evaluation Tests

Drug absorption from the colon can be monitored by colonoscopy and intubation.Gammascintigraphy and high frequency capsules are now the most used methods for evaluating colon medication delivery systems.

Gamma Scintigraphy:

The transit time of a dose form via the GIT can be tested and monitored using this technique.The use of gamma scintigraphy in pharmacokinetic research aids in the identification of drug absorption sites.A crystal collimates and detects the gamma radiations emitted by the patient.The energy is converted to light scintillation and intensified before being digitalized.This procedure is non-invasive, and it can be used on patients with low levels of radiation.Food passage and gastric emptying of dose forms can also be evaluated.This approach also allows for visualisation of the drug distribution process.

High Frequency Capsule Method

This method is used to examine drug absorption qualities in the colon.High frequency capsules can be used to assess the relative bioavailability of colonic medication delivery methods.The advantages of this are that relative bioavailability from any GIT site may be assessed, and drug release at several GIT sites within the same item can be utilised to compare absorption properties.

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Table .2- Techniques Employed In Marketed Drugs.

Techniques Employed	Polymers used	Drugs used	Reference
pH dependent	Eudragit L100&S 100	Mesalazine, Diclofenac sodium&5-ASA	20
	Eudragit S, Eudragit FS, Eudragit P4135F	Prednisolone	21
	Eudragit L 30D55,Eudragit FS 30D	Paracetamol	22
Time dependent	Hydroxy propyl methyl cellulose	Pseudoephedrine HCL	23
	Hydroxyethyl cellulose, Ethyl cellulose	Theophylline	24
	Microcrystalline cellulose, Lactose or Behinic acid	Indomethacin	25
Bacteria dependent or Polysaccharide based	Chitosan	Diclofenac Sodium	26
	Pectin	Indomethacin	27
	Guargum	Dexamethasone	28

Table 3-Formulation and Doses Of Marketed Drugs.

Drug	Trade Name	Formulation	Dose	Reference
1.Mesalamine	Asacol	Eudragit `s' coated tablets	0.8-2.4g/day	53
2.Mesalamine	Salotac	Eudragit `s' coated	1-4g/day	53
3.Mesalamine	Pentaza	Controlled release EC coated tablets	1.5-4g/day	53
4.Mesalamine	Claversal	Eudragit `L' coated tablets	1-2g/day	53
5.Budenoside	Entocort	Eudragit `L' coated tablets	9mg/day	53
6.Olasalazine	Dipentum	5-ASA dimer as capsules and tablets	1g/day	53
7.Sulfasalazine	Salazopyrin	5-ASA linked to sulfapyridine as tablet	1-2g/day	53

II. CONCLUSION

Drug administration to the diseased colon is advantageous in terms of avoiding systemic adverse effects, lowering drug doses, only supplying the drug when it is needed, and keeping the drug in its intact form as close to the target site as feasible.Better colonic delivery could be obtained by protecting the drug from absorption and/or the upper GIT environment before rapidly releasing it into the proximal colon, which is the site for colonic targeted drug delivery.All of the methods can be used to treat local disorders of the colon or to improve systemic absorption of poorly absorbed medications.Microflora found in the colon could be used to target drug release in the colon.

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