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A COMPRENSIVE REVIEW ON COLON TARGETED DRUG DELIVER SYSTEM

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➢ ABSTRACT

The oral route is considered to be the most preferred route for administration of drugs for systemic effect, but the oral route is not suitable to the administration of drug for lower gastrointestinal (GI) diseases, this happened due to their release at upper GI tract (stomach, small intestine), which further minimizes the accessibility of drugs at the lower GI tract. To overcome this difficulty, colon-specific drug delivery systems have been broadly analysed during the last two decades. Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, etc. but also for the systemic delivery of proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs, and anti-diabetic agents. This review article discusses, in brief, the introduction of the colon, factor affecting the colonic transition, colonic diseases and the novel and emerging technologies for colon targeting.

Key Words: Colon drug delivery, Crohn's disease, inflammatory bowel disease, Lower GI tract, Eudragit S 100

➢ INTRODUCTION

The aim of a targeted drug delivery system is to provide a desired drug concentration in the body by delivering a therapeutic amount of drug to a target site. It is suitable and required for the drugs having instability, low solubility, and short half-life, a large volume of distribution, poor absorption, low specificity, and therapeutic index. Targeting may provide maximum therapeutic activity (by preventing degradation or inactivation of drug). Meanwhile, it can also minimize adverse effects, the toxicity of potent drugs by reducing dose. The oral route is the most convenient and important method for administration of drugs for systemic effect.

In addition, less pain, reduced risk of cross infection, needle stick injuries, patient acceptance and ease of administration made it more preferred. Nearly 50% of the drug delivery systems available in the market are oral drug delivery systems. Apart of these advantages, the oral route is not suitable to the administration of the drug for lower gastrointestinal (GI) diseases; this happened due to their release at upper GI tract (stomach, small intestine), which further minimizes the accessibility of drugs at the lower GI tract.

To overcome this difficulty, colon-specific drug delivery systems have been broadly analyse during the last two decades. By definition, a colonic delivery refers to delivery of drugs accurately into the lower GI tract (by avoiding the drug release in upper GIT), which occurs primarily in the large intestine (i.e. colon). Rectal administration is another route used for colon targeting, but it shows less compliance (uncomfortable) and becomes difficult to reach the colon. Conventional dosage forms that are used in the prevention of colon diseases (ulcerative colitis, crohn's diseases, and amoebiasis) are failing as an improper amount of drug reaches site of action. Conventional dosage form affords the drug to be absorbed from the upper part of GIT, i.e., stomach. This action of conventional dosage form has a serious drawback for colonic localized delivery. Thus, for efficient and safe therapy, the drug is needed to be preserve from upper hostile environment.

Site-specific delivery into the colon is not only needed for local treatment of a variety of colon diseases, like ulcerative colitis, Chron's diseases, amoebiasis, colon cancer, but also systemic delivery of proteins and peptides this is because of less diversity and intensity of digestive enzymes and less proteolytic activity of colon mucosa than that observed in the small intestine. Beside the colon diseases, this system is also helpful in the treatment of asthma, angina and rheumatoid arthritis for taking advantage of Chrono therapeutic drug delivery and for delivery of steroids.

Some factors to be considered for successful colonic drug delivery, including the properties of the drug, the type of delivery system and its interaction with healthy or disease gut. The longer residence time, less peptidase activity, natural absorptive characteristics and high response to absorption enhancers make it most promising site for drug delivery. The absorption enhancers are sub characterized into categories of chelating agents, non-steroidal anti-inflammatory agents, surfactants (mostly as mixed micelles), phenothiazine and a

general class of molecules which include fatty acids, acylcarnitiveacyl amino acids and dicarboxylic acid.

Advantages

1. Ideal site for the delivery of active agents to cure the colon diseases like chron's disease, ulcerative colitis, amoebiasis.

2. Smaller drug quantities should be required for local treatment.

3. Less side effects and drug interactions occurs.

4. Dosage frequency is less so, cost effective.

5. The long retention time of colon, improved bioavailability of poorly absorbed drug molecules (up to 5 days).

6. Reduce gastric irritation caused by many drugs by preventing their absorption in upper GIT (e.g., NSAIDS).

7. Bypass initial first pass metabolism.

8. Extended daytime or night time activity.

9. Hard accessibility of the colon because of its location at the distal part of the alimentary canal.

10. The drug may bind non-specifically to intestinal contents (dietary residues, intestinal secretions, faecal matter) cause reduce drugs bioavailability.

11. Metabolic degradation of the drug by resident microflora could also affect colonic performance.

12. Restrict drug transport across the mucosa and into the systemic circulation due to lower surface area and relative tight junctions in the colon.

13. Lack of an appropriate dissolution testing method to evaluate the dosage form in-vitro.

14. The drug in solution form required for successful colon delivery or alternatively, it should dissolve in the luminal fluids of the colon, but this can be a limiting factor for poorly soluble drugs.

15. Factors to be considered in the design of colon specific drug delivery system.

16. Anatomy and physiology of colon

The GIT (alimentary canal) is a muscular, digestive tube that extends from mouth to anus, having functions to digest dietary food, to absorb nutrients, electrolytes, and fluids, and to prevent the absorption of potentially harmful substances.

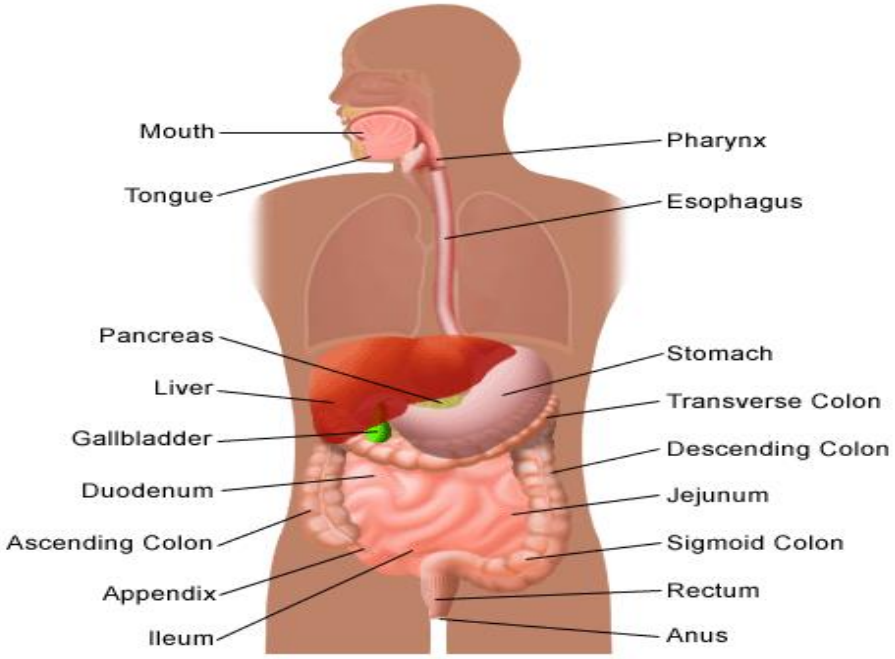

Fig.1

The GI tract is divided into stomach, small intestine, and large intestine. The longest part of the GIT is small intestine where most enzymatic digestion and absorption occur. The large intestine is the last major portion of the GIT (starts from the distal end of the ileum to the anus) and is about 1.5 m long.

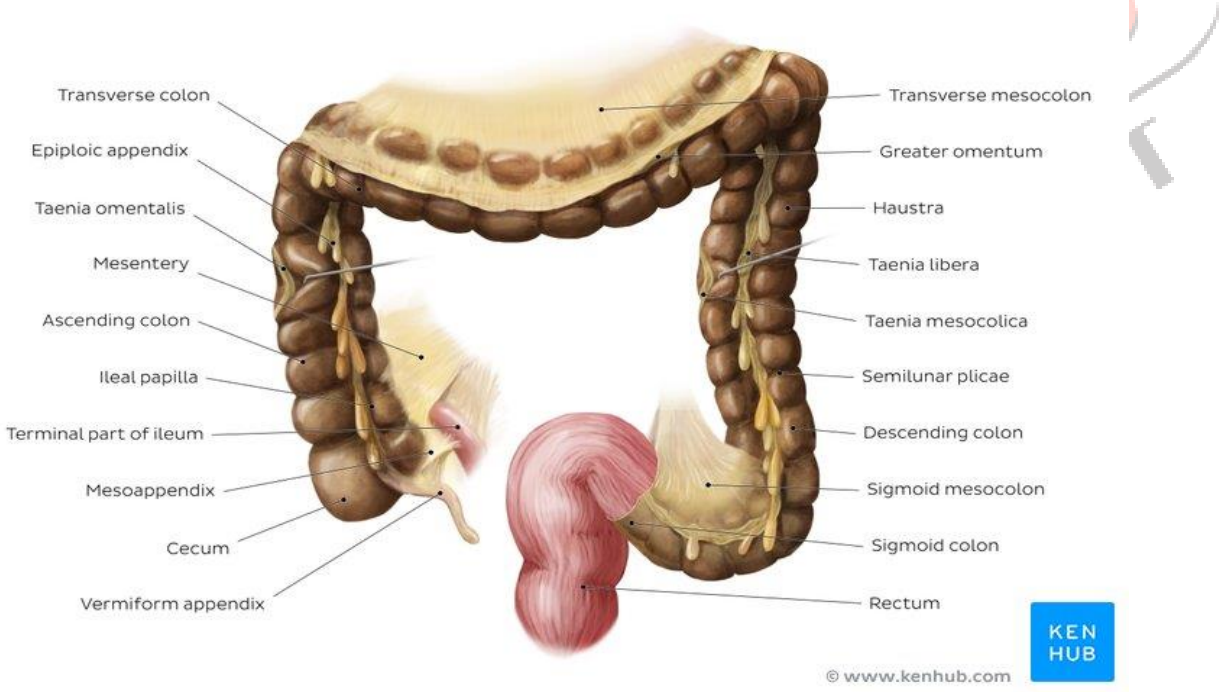

Fig.2

Colon is upper five feet of the large intestine and mainly situated in the abdomen. Colon is a cylindrical tube that is lined by mucosa. The cecum is the first part of the colon and leads to the right colon or the ascending colon followed by the transverse colon, the descending colon, sigmoid colon, rectum and the anal canal. The right colon is made up of the cecum, ascending colon, hepatic flexure and the right half of the transverse colon and left colon is made up of the left half of the transverse colon, splenic flexure, descending colon, and

sigmoid. The colon does not have villi unlike small intestine, but due to the presence of plicaesemilunares (crescentic folds) the intestinal surface of the colon is increased to approximately 1300 cm^2.

Structure of colon

The colon is made up of different layers and parts.

Table no.1. Different layer and part of colon

Layers of colon	**Description**
Serosa Muscular external Submucosa Mucosa	• Exterior coat of the large intestine. • Major muscular coat of the large intestine which composed of an inner circular layer of fibers surrounding the bowel and an outer longitudinal layer. • A layer of connective tissue lies immediately beneath mucosa lining the lumen of the colon. • The mucosa has three parts: epithelium, lamina propria, and muscular mucosa
Parts of colon	**Description**
Ascending colon Cecum(Proximal right colon) Transverse right colon Descending colon Sigmoid colon Rectum Anal canal	• 20–25cm long located behind the peritoneum hepatic flexure lies under right lobe of the liver • 20–25cm long located behind the peritoneum hepatic flexure lies under right lobe of the liver • Lies anterior in the abdomen, attached to gastro colic ligament splenic flexure near tail of pancreas and spleen • 10–15cm long located behind the peritoneum. After it enters the true pelvis it is known as the sigmoid colon • This part describes an S-shaped curve in the pelvis that continues downwards to become the rectum • This is a slightly dilated section of the colon about 13cm long. It leads from the sigmoid colon and terminates in the anal canal • This is short passage 3.8 cm long and leads from rectum to the exterior

Function of colon:

- The consolidation of the intestinal contents into feces by the absorption of the water and electrolytes and storage of feces until excreted from the body.
- To provide a favourable environment for the growth of colonic microorganisms.
- Absorption of H2O and Na+ from the lumen, and secretion of K+ and HCO3.

Physiological Factor and Pharmaceutical Factor

Colonic pH: The pH of the gastrointestinal tract is subject to both inter and intra subject variations. This pH variability of the GIT has been used as a means for targeted colon drug delivery and influenced by some factors like diet, diseased state and food intake. Due to the presence of short chain fatty acids (bacterial fermentation of poly saccharides), fall in pH into the colon.

Table no.2

The region of GIT tract		Length (cm)	pH	Internal diameter(cm)
Stomach		-----	1.2-3 (fastest) 2-5(fed)	------
Small intestine	Duodenum	20-30	≈6.1(fastest) ≈5.4(fed)	3-4
	Jejunum	150-200	≈5.4	
	Ileum	200-350	7-8	
Large intestine	cecum	6-7	≈5.5-7	6
colon	Ascending	20	7-8	
	Transverse	45		
	Descending	30		
	Sigmoid	40		
Rectum		12		
Anal canal		3		

Transit of material in the Colon: The factors, rate of gastric emptying and the small intestinal transit time influence the delivery of an oral dosage form

Table no.3

Organ	Transit time(h)
Stomach	<1(fasting) >3(fed)
Small intestine	3-4
Large intestine	20-30

Colonic Microflora and Enzyme: In colon around 400 distinct bacterial species have been found with concentration 10^{11} -10^{12} CFU/ml, of which 20-30% belongs to genus Bacteroides. Variety of microorganism present throughout the GIT, which further produces enzymes for a metabolic activity like hydrolysis, decarboxylation, dealkylation. The bacterial count (Colony forming unit CFU/ml) in different regions of the GIT is 0-10^3 CFU/ml in stomach, 0-10^5 CFU/ml in jejunum and 10^3 -10^7 CFU/ml in ileum.

Table no.4

Enzyme	Microorganism	Metabolic reaction-catalysed
Nitro reductase	E. coli, Bacteroides	Reduce aromatic and heterocyclic nitro compounds
Azoreductase	Clostridia, Lactobacilli, E. coli	Reductive cleavage of azo compounds
Glycosidase	Clostridia, Eubacterium	Cleavage of β-glycosidase of alcohols and phenols
Glucuronidase	E. coli, A. aerogenes	Cleavage of β-glucuronidases of alcohols and phenols

Pharmaceutical Factor

Drug Candidates:

- It should poorly absorb from the stomach and small intestine.
- It should show compatibility with carrier molecule and show stability at alkaline pH of GIT.
- It should be used in the treatment of various colon disorders.

Drug Carrier:

The carrier selection depends on the physiochemical nature of the drug as well as the disease for which the system is to be used, other factors such as chemical nature, stability and partition coefficient of drug and the type of absorption enhancers chosen.

Colonic Absorption of Drug:

Absorption of drugs from colon takes place either transcellular or paracellular route. Drugs well absorbed from colon include glibenclamide, diclofenac, theophylline and ibuprofen. Drugs shown to be less absorbed from colon include furosemide, piretanide, buflomedil, atenolol, cimetidine, lithium and ciprofloxacin.

Approaches used for Site-Specific Drug Delivery to Colon (CDDS):

Primary Approaches for CDDS:

pH Sensitive Polymer Coated Drug Delivery to Colon:

Principal: Provide coating to the dosage form (e.g., tablets/pellets, etc.) with various pH sensitive polymers which will produce delayed release formulation and protect it from upper GIT. Most commonly used pH-dependent coating polymers are methacrylic acid

copolymers, commonly known as Eudragit S, more specifically Eudragit L and S. These polymers shows insolubility at low pH levels but become increasingly soluble as pH rise.

Some problems associated with this approach are:

• Variability in gastrointestinal pH between and within individuals and is affected by diet and disease conditions.

• Poor site-specificity (start to dissolve even in the lower small intestine).

Delayed (Time-Controlled Release System) Release Drug Delivery to Colon:

Principle: Drug release from dosage form should be after a predetermined lag time, i.e., delivers the drug at the right site of action at the right time and in the right amount, Lag time≈5 h. Zein was proved to be a potential coating material for a delayed release of drug to colon.

Disadvantages: Variability in gastric emptying time between subjects and depend on type and amount of food intake and gastrointestinal movement.

Example: Enteric-coated time-release press coated tablets.

Microbially Triggered Drug Delivery to Colon:

Principle: Drug release in colon via degradation of biodegradable polymers coated on the dosage forms by microflora present in colon, because colon is rich in microorganisms. These dosage form protected from upper GIT, due to very little microbial degradable activity in upper GIT is present which is insufficient for cleavage of the polymer coating.

A. Prodrug Approach for Drug Delivery to Colon: For colonic delivery, the prodrug (a pharmacologically inactive derivative of a parent drug molecule) is designed to undergo minimal hydrolysis in the upper tracts of GIT, and undergo enzymatic hydrolysis in the colon there by releasing the active drug moiety from the drug carrier.

Limitations:

• No versatile approach as its formulation depends upon the functional group available on the drug moiety for chemical linkage.

• Need a lot of evaluation before being used as carriers.

Azo-Polymeric Prodrugs: Sub-synthetic polymers form a polymeric prodrug with azo linkage between the polymer and drug moiety. Azo polymers have been found to be susceptible to cleavage by the azoreductase in the large bowel.

B. Polysaccharide-Based Delivery System: Naturally occurring polysaccharides is used for targeting the colon and found in abundance, inexpensive and are available in a variety of structures with varied properties. They can be easily modified chemically, and are highly

stable, safe, non-toxic, hydrophilic and biodegradable. These polysaccharides are obtained from the plant (guar gum, inulin), animal (chitosan, chondroitin sulphate), algal (alginates) or microbial (dextran) origin. The polysaccharides can be broken down by the colonic microflora to simple saccharides. Therefore, they fall into the category of "generally regarded as safe" (GRAS).

Newly Developed Approaches for CDDS:

Pressure Controlled Drug-Delivery Systems: Contractile activity of the stomach and peristaltic movements for propulsion of intestinal contents required for the digestive process. The pressure generated by muscular contraction of the gut wall is responsible for the grinding and propulsion of the intestinal contents, and changes in the intensity and duration throughout the GI tract, while the colon is considered to have higher luminal pressure due to the process that occurs during stool formation.

Pulsatile Colon Targeted Drug Delivery:

1) Pulsincap System: These (single-unit) systems are mostly developed in a capsule form. The drug is released as a "Pulse" from the insoluble capsule body by swelling or erosion of plug (control lag time). A swellable hydrogel plug was used to seal the drug contents into the capsule body, and when in contact with the dissolution fluid, it swells, and after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug. The length of the plug and its point of insertion into the capsule controls the lag time.

2) Port System: This system based on the principle of delayed drug release. This system consists of:

- Gelatine capsule coated with a semi-permeable membrane (e.g., cellulose acetate) housing,
- An insoluble plug (e.g., lipidic),
- An osmotically active agent along with the drug formulation.

Novel Colon Targeted Delivery System (CODESTM): CODESTM is a unique CDDS technology and overcomes problems associated with pH or time-dependent systems. It is a combined approach of pH-dependent and microbially triggered CDDS. A unique mechanism involving lactulose acts as a trigger for site-specific drug release in the colon.

Osmotic Controlled Drug Delivery (ORDS-CT): The OROS-CT (Alzacorporation) has been used to target the drug locally to the colon . Drug release begins when the unit reached the colon and maintained a constant release rate for up to 24 h in the colon.

Multiparticulate System: These formulations consist some minute independent subunits containing active ingredients and are developed by time-controlled explosion system in which drug release is caused by the explosion of a membrane after a definite period which is precisely programmed. It includes formulations such as pellets, granules, microparticles, nanoparticles, and beads.

Potential benefits of multiparticulate system:

• Quick delivery, long duration of action, hence increased bioavailability.

• Uniformly dispersed in the GI tract and ensure uniform drug absorption.

• Reduced risk of systemic toxicity, local irritation and predictable gastric emptying.

Pro-biotic Approach: The modern techniques for colon targeting required three components namely probiotic strain (Bifidobacterium and Lacto bacillus), microbial digestible carrier and triggered temperature. These strains triggered to be active at body temperature and the breakdown of carrier take place and lastly release the drug at the desired place. This approach gains success because of the availability of these conditions in colon.

Evaluation of Colon-Specific Delivery: No standardized evaluation technique for CDDS is available because an ideal in-vitro model should possess the in-vivo conditions of GIT such as pH, volume, bacteria, enzymes, enzyme activity and other components of food and these conditions are influenced by the diet and physical stress.

In-vitro Dissolution Test: Conventional basket method may be used for CDDS. Enteric-coated capsules for CDDS have been investigated in three buffers. The capsules were tested for two hours at pH 1.2, then 1 h at pH 6.8 and finally at pH 7.4. Dissolution Testing of Polysaccharide-Based Colon-Specific Drug Delivery: 16 The most commonly used dissolution testing methods for these delivery systems involve the addition of enzymes, rat caecal contents and human faecal slurries.

In-vitro Enzymatic Test:

These are 2 tests for the in-vitro enzymatic test. ϖ Incubation of carrier drug system in a fermenter having a suitable medium for bacteria and determine the amount of drug release at various time intervals.

Incubation of carrier drug system in buffer medium containing enzymes pectinase, dextranase or rat or guinea pig or rabbit caecal contents and determine the amount of drug released in a specific time, i.e., directly proportional to the rate of degradation of the polymer.

In-vivo Evaluation: The in-vivo evaluation of the CDDS is done in dog's guinea pigs, rats, and pigs because of the resemblance of anatomic and physiological conditions micro, flora of human GIT, the distribution of various enzymes in GIT of rat and rabbit is comparable to that in human.

TABLE 3: MARKETED DRUG PRODUCTS FOR THE TREATMENT OF VARIOUS DISEASES OF COLON

Sr.no	Marketed Name	Company name	Disease	Drug
1	Mesacol tablet	Sun Pharma, India	Ulcerative colitis	Mesalamine
2	Asacol	Winmedicare, India	Ulcerative colitis, crohn's disease	Mesalamine
3	SAZO	Wallace, India	Ulcerative colitis, crohn's disease	Sulphasalazine
4	Intazide	Intas, India	Ulcerative colitis	Balasazide
5	COLOSPA	Solvay, India	Irritable colon syndrome	Mebeverine
6	CYCLOMI NOL	Neol, India	Irritable colon syndrome	Diclomine

Colonic Specific Polymer:

1. Guar gum: Guar gum is used in colon targeted drug delivery systems due to its drug release retarding property and susceptibility to microbial degradation in large intestine.

2. Xanthan gum: Xanthan is a free-flowing powder, give viscous solutions at low concentrations and offer very good stability. Xanthan gum and hydroxypropyl methylcellulose were used as hydrophilic matrix agents for preparing modified release tablets of diltiazem HCl.

3. Alginate: Alginates are linear polymers.

4. Cellulose Acetate Phthalate: Cellulose acetate phthalate was synthesized in 1940 by Hiatt and was one of the first polymers used for its enteric properties. The CAP polymer exhibits rapid dissolution at a pH >6. The addition of a plasticizing agent (Diethyl phthalate triacetin) has been shown to improve the water resistance of CAP films. It is practically insoluble in water and ethanol; soluble in acetone. CAP concentrations in oral formulations are typically limited to 0.5-0.9% of the tablet core weight.

CONCLUSION: Colon targeted drug delivery system generate both local and systemic effects. The main advantage of colon drug delivery system is, long transit time, near neutral pH, reduced enzymatic activity and increased responsiveness to absorption enhancers. The main aim of CDDS is to preserve the formulation during its transit through the stomach and small intestine. There are some novel approaches more specific compared to primary approaches like pressure controlled drug delivery system, pulsincap system, port system;

colon-targeted delivery system (CODES), multiparticulate system and pro-biotic. Both polysaccharides and synthetic polymers are used for the colon targeting. The colon targeted drug delivery provides safe, effective and less expensive delivery of drugs with minimum fluctuation at the target site.

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