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COLON TARGETED DRUG DELIVERY SYSTEM: A REVIEW

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Abstract

Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amoebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs. To achieve successful colon targeted drug delivery, a drug need to be protected from degradation, release and absorption in upper portion of the GI tract and then to be ensured abrupt or controlled release in the proximal colon. This review is focused on the merits and demerits, novel approaches in the colon targeted drug delivery, clinical evaluation techniques and some information on the marketed dosage forms.

Keywords: Colonic drug delivery, Drug targeting, novel approaches, gamma scintigraphy.

Introduction

Colon delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e. Colon).[1] The site specific delivery of drugs to lower parts of GIT is advantageous for localized treatment of several colonic diseases, mainly inflammatory bowel disease (crohn's disease and ulcerative colitis), Irritable bowel syndrome and colon cancer. The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons; (i) less diversity, and intensity of digestive enzymes, (ii) comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CTDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the

drug into ileum or colon which leads to greater systemic bioavailability. Oral controlled release formulations for the small intestine and colon have received considerable attention in the past 25 years for a variety of reasons including pharmaceutical superiority and clinical benefits derived from the drug release pattern that are not achieved with traditional immediate or sustained release products.[2]. Colon drug delivery has also gained increased importance not just for the systemic delivery of drugs for the treatment of local diseases, but also potential site for the systemic delivery of therapeutic proteins and peptides which are being delivered by injections. These delivery systems when taken orally, allow drugs to release the drug from the delivery system once the drug reaches in to the colon. [3, 4]

Need of Colon Targeted Drug Delivery

Targeted drug delivery into the colon helpful in treatment of diseases at that site, fewer systemic side effects and dose can be minimized.

Colon specific formulation is beneficial for the administration of proteins, peptide drugs and also to prolong the drug delivery.

Colon targeted drug delivery is suitable for delivery of drugs which are polar and/or susceptible to the chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism

Serious diseases of the colon are treated more effectively if drugs were targeted to the colon.

Example. Colonic cancers like colorectal cancer. [5,6]

Anatomy of Colon
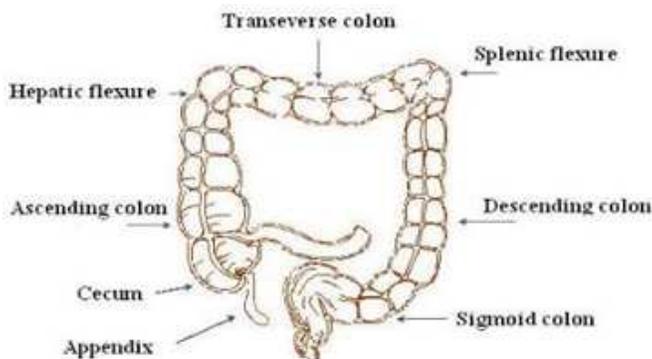
fig 1: Colon and its segments

The entire colon is about 5 feet (150 cm) long and is divided into 5 major segments. The GI tract is divided into stomach, small intestine and large intestine. Large intestine extending from the ileocecal junction to the anus and it is divided into 3 main parts. (Figure - 1) They are colon, rectum, and anal canal. Perinatal folds are called as mesentery which is supported by ascending and descending colon. The right colon consists of the cecum, ascending colon and hepatic flexure. The left colon consists of descending colon, splenic flexure and sigmoid. The rectum is the last anatomic segment before the anus .The colon tissue contains the villi, lymph, muscle, nerves and vessels. The absorptive capacity is very high, each about 2000ml of fluid enters the colon through the ileocecal valve from which 90% of fluid is absorbed. The adult colon is line by atleast 8 distinct epithelial cell types, viz columnar or absorptive cells, deep crypt secretary cells, vacuolated cells, microfold or M cells, undifferentiated crypt cells, multivesicular or caveolated cells, goblet cellsand variety of endocrine cells. [3,5,7]

Advantages

- The site specific delivery of drugs to lower parts of the GI tract is advantageous for localized treatment of several colonic diseases, mainly inflammatory bowel disease, irritable bowel syndrome, colon cancer

- Used in treatment of nicotinic addiction

- Useful for the delivery of proteins, peptides which are being delivered by injections

- Delayed mechanisms are designed to improve the efficacy of the drug by concentrating the drug molecules where they are need most and also minimize the potential side effects and drug instability

- Used in direct treatment of disease at that site ,low dosing and less systemic side effects

- Molecules that are poorly absorbed in the upper gut, such as peptides, proteins may be better absorbed from the lower GIT.

- The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease.

- The colon is having high water absorption capacity, the colonic contents are considerably viscous and thus availability of most drugs to the absorptive membrane is low.

- The metabolic processes like azoreduction and enzymatic cleavage are takes place in colon which is responsible for the metabolism of many drugs and peptides like insulin. [7,8,9]

Disadvantages

- A longer residence time of 3-5 days results in elevated plasma levels of the drugs and therefore higher bioavailability in general, but especially for drugs that are substrates for this class of enzyme.

- Single unit colon targeted drug delivery system has the disadvantage of un intentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology

- Development of colon specific drug is difficult due to many biological barriers

- Cytochrome (P450) class of drug metabolizing enzymes has lower affinity in the colonic mucosa. [8,10]

Limitations

- Colon offers a near neutral pH, at the site of drug delivery ,reduced enzyme activity ,a long transit time and increased responsiveness to absorption enhancers

- Wide range of pH values and different enzymes present throughout the gastro intestinal tract, through which dosage form has to travel before reaching target site

- For better drug delivery it should be in solution form before it arrives in the colon

- Fluid content in the colon is much lower and it is more viscous than in the upper part of GI tract.

- Stability of drug is also a concern and must be taken into consideration while designing the delivery system. The drug may potentially bind in a non-specific way to dietary residues ,intestinal secretions ,mucus or fecal matter

- The resident microflora could also affect colonic performance via metabolic degradation of the drug

- Lower surface area and relative tightness also affects the bioavailability of drugs. [7,8]

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

Gastrointestinal motility in fasted state proceeds through 4 phase over a period of 2-3 hours. The feeding state affects the normal pattern by irregular contractile activity.

Small Intestinal Transit

Small intestinal transit is not influenced by the physical state, size of the dosage form and the presence of food in the stomach. The mean transit time of the dosage form is about 3-4 hours to reach the ileocecal junction and the time period is consistent.

Colonic Transit

The bioavailability of drugs released from the dosage forms can be highly influenced by the colonic transit time. Various factors like gender and size of the dosage form and physiological conditions such as stress, presence of food and diseased state influence the colonic transit time. Small particles and solutions pass slowly through the proximal colon and in human being, Men shows shorter colonic transit time than women. The colonic transit time of capsule in adults is 20-35 hours, the transit time of capsule is independent of the capsule density and volume.

Gastric Emptying

Gastric emptying is fastest and most consistent. Emptying completes from 5-10 min up to 2 hrs, depending on phase of stomach at the time of drug administration. Gastric emptying can be considerably slowed by fed state.

Stomach and Intestinal pH

Release and absorption of orally administered drugs are influenced by the gastro intestinal pH. (Table-1)

Table -1: pH of GIT at various sites.

S.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

The human alimentary canal is highly populated with bacteria and other microflora at both ends, are oral cavity and the colon /rectum. Azoreductase produced by the colonic microflora plays an important role in development of a number of delivery systems, particularly in catalyzing the release of 5-amino salicylic acid, from a variety of prodrugs. Other enzymes are glycosidase and glucuronidases produced by lactobacilli, bacteroids and bifidobacteria. The activity of enzyme is associated with the concentration of bacteria in particular region.

Colonic Absorption

The surface area of colon is much less compared to small intestine, and hence not ideally suited for absorption. Colon is considered for drug delivery because the environment is dividing of endogenous enzymes other than microbial origin. Resident time of colon is 10-24 hours. Little mixing in the colon makes it possible to create local environments with optimal absorption. Absorption is influenced by the transport of water, electrolytes and ammonia across the mucosa and it as more in the proximal colon and distal colon.

Mechanisms of Absorptions

- Passing through colonocytes (trancellular transport)

- Passing between adjacent colonocytes(paracellular transport)

Absorption enhancers facilitate effective absorption through various mechanisms .They are disruption of the intracellular occluding junction complex opens the paracellular route, modification of epithelial permeability by denaturing membrane proteins and modification of lipid protein interactions and disruption of the integrity of lipid barrier by colonic enterocytes.

Colonic Absorption of Macromolecules

The absorption property of Bovine serum albumin is 0.13% from colon and 1.7% through small intestine. This is due to surface area difference.

Gastrointestinal Diseased State: Crohn's disease, constipation, diarrhea and gastroenteritis may affect the release and absorption properties of colon specific drug delivery systems.

Pharmaceutical Factors

Drug Molecules

Drugs which show poor absorption from the stomach or intestine including peptide drugs are most suitable for colon specific drug delivery systems. Sulphasalazine and 5-ASA are widely used drugs for treatment of IBD and other diseases.

Drug Carriers

The selection of carrier for particular drug candidate depends on physicochemical nature of drug as well as disease for which the system is to be used. Chemicalnature, stability and partition coefficient of the drug and type of absorption enhancer chosen influence the carrier selection. [7,11,12]

Targeting Approaches to Colon

Colon specific drug delivery is considered as beneficial in the treatment of colon related diseases and the oral delivery of protein and peptide drugs. Various mechanisms following for colon targeted drug delivery are :

   i) Coating with pH dependent polymers

   ii) Osmotic control system

   iii) Pressure delivery systems

    iv)   Coating with pH independent biodegradable polymers

    v)   Delivery systems based on the metabolic activity of colonic bacteria

    vi)   Pulsating drug delivery system

    vii)   Time controlled or time dependent system

Coating With pH Dependent Bio Degradable Polymers

Bio degradable azo polymers with high hydrophilicity exhibit superior degradation properties and are used to coat

capsules. Higher degree of hydrophilicity may cause the drug release from the system before it reaches the colon. The

azo polymer systems are not suitable for delivery of peptides, hormones and other drugs with a narrow therapeutic

index; however they are suitable for local delivery of drugs to colon. Most commonly used polymers are methacrylic

acid co polymers commonly known as eudragit L and eudragit S. Carboxyl polymer form salts and dissolves at pH5.5

and disperse in water to form latex and thus avoid the use of organic solvents in the coating processes.

The working principle of biodegradable azo polymer systems was shown in Figure .2.
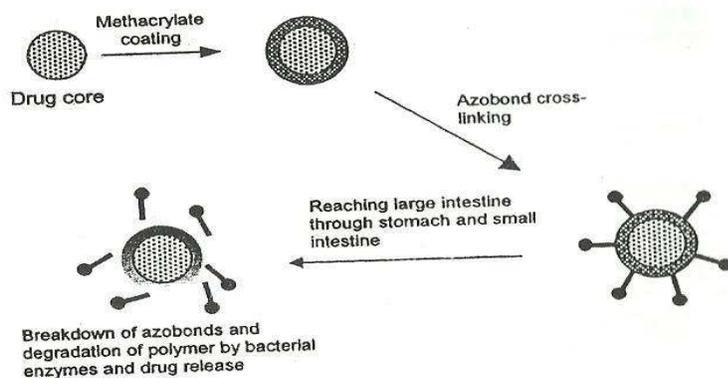
Figure-2: Working principle of biodegradable azo polymer systems.

Osmotic Controlled System (ORDS-CT)

The ORDS-CT (Alza Corporation) system can be a single osmotic unit or may incorporate as many as 5-6 push-pull

units, each 4mm in diameter, encapsulated with in a hard gelatin capsule. Each bilayer push-pull unit contains an

osmotic push layer and a drug layer, both surrounded by a semipermeable membrane (Fig.3). As the unit enters small intestine the coating dissolves in this higher pH environment compartment.
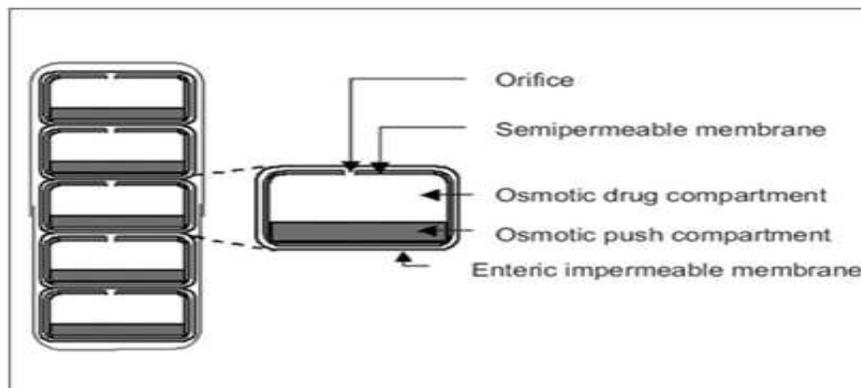

fig 3: Cross section of the OROS-CT colon targeted drug delivery system

Mechanism

The muscular contractions of the gut wall generate pressure, which is responsible for grinding and propulsion of the intestinal contents .This pressure is responsible for release of drug from the capsule shell.

Pressure Controlled System

Luminar pressure within the colon, which forms the basis for design of pressure control systems .The particular delivery, is in the form of capsule which is resistant to the pressures of upper GIT but it is collapsed in the large intestine due to increased pressure. The digestive processes within the GI tract involve contractile activity of the stomach and peristaltic movements for propulsion of intestinal contents. These strong peristaltic waves in the colon are of short duration, occurring only 3-4 times a day. The capsule shells are fabricated from ethyl cellulose and the collapse time of the capsule in large intestine can be controlled by adjusting the thickness of the capsule shell wall.

COATING WITH PH INDEPENDENT BIODEGRADABLE POLYMERS

Drugs that are coated with polymers, which are showing degradability due to the influence of colonic microorganisms, can be exploited in designing drugs for colon targeting in order to release an orally administered drug in colon.

The copolymers of styrene and 2- Hydroxyl Methyl Methacrylate were cross linked with divinylazo benzene to coat oral dosage forms of insulin and vasopressin. The intestinal microflora has a large metabolic capacity and it appears that reduction of azobonds is a general reaction of colonic bacteria.

DELIVERY OF DRUGS BASED ON METABOLIC ACTIVITY OF MICROFLORA

Prodrugs

Prodrug design often represents a nonspecific chemical approach to mask unwanted drug properties such as low bioavailability, less site specificity and chemical in stability. Prodrugs targeting to a specific enzyme or a specific membrane transporter or both have potential drug delivery system especially for colon cancer chemotherapy.

Example- Sulphasalazine in treatment of ulcerative colitis and Crohn's disease.

Hydrogels

Hydrogels contain acidic co-monomers and enzymatic degradable azo aromatic cross links. A number of drug delivery systems have been proposed to deliver the drug for efficient therapy. The controlled release of active anti-microbial agents from the polymeric matrix has been well reported.

Example- Amoxicillin, Metronidazole, Oxytetracycline, Tetracycline-HCL

Pulsating Drug Delivery

In pulsating drug delivery, the drug is released rapidly after a well-defined lag time. The lag time prior to rupture is mainly controlled by the permeation, mechanical properties of the polymer coating and the swelling behavior of the swelling layer

Methods for pulsatile drug delivery systems are capsular system, Osmotic system, solubilisation or erosion of membrane and rupture of membrane.

Time Control/Dependent Systems

Time dependent process is useful for synchronous delivery of a drug. Transit time through the small intestine is independent of type of formulation (Fig 4). Effects of variance in gastric resident time can be minimized by using systems that are protected in the stomach and drug release can be targeted on the colon by means of formulations that

release drug after a certain time of gastric emptying. Combinations of hydrophilic(HPMC) and hydrophobic polymers have been used as coatings for tablets that release drug from a core after a lag time. Time controlled formulations have also been prepared using water insoluble ethylcellulose and swellable polymer.[7, 11-17]
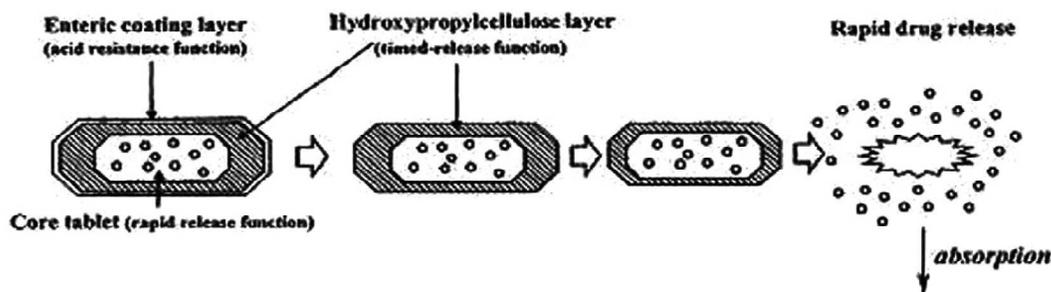
FIG 4: Design Of Enteric Coated Timed-Release Press Coated Tablet(ETP Tablet).

Evaluation Tests

There is different in-*vitro* methods are used to evaluate different carrier systems for their ability to deliver drugs specifically to the colon.

Invitro Dissolution Tests

Ability of coats or carriers to remain intact in stomach and small intestine is generally assessed by conducting drug release studies in 0.1NHCl for 2hrs.The conventional method involving dissolution in various buffers is useful for assessing the ability of an enteric coating to prevent drug release in the stomach and small intestine. Dissolution tests relating to colon specific drug delivery systems may be carried out by using the conventional basket method. The media chosen were, for example pH 1.2-stimulate gastricfluid, 6.8-jejunal region, 7.2-ileal segment.

Invivo Evaluation Tests

Guineapigs, dogs, pigs and rats are generally used to evaluate the drug delivery to colon as they have anatomical and physiological similarities. Human fetal bowel is transported into a subcutaneous tulle on the back of the thyme nude mice, which vascularizes within 4weeks,matures and capable of developing of mucosal immune system from the host.
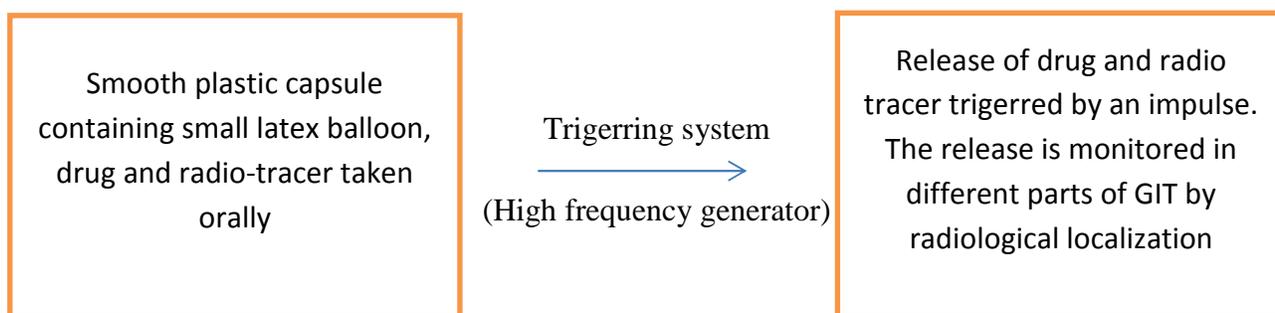
Clinical Evaluation Tests

Colonoscopy and intubation can be used to monitor the absorption of drugs from the colon. At present gammascintigraphy and high frequency capsules are the most preferred techniques used to evaluate colon drug delivery systems.

Gamma Scintigraphy:

By using this technique, the transit time of dosage form through the GIT can be measured and monitored. * The pharmacokinetic studies by adopting gamma scintigraphyhelps to identify the sites of drug absorption. The gamma radiations emerging from the subject are collimated and detected by a crystal. The energy is transformed to light scintillation and amplified to give digitalized results. This technique is non-invasive and even low radiation in patients can successfully be used. Gastric emptying of dosage forms and transit of food can also be measured. Visualization of the drug delivery process is also possible with this technique.

High Frequency Capsule Method

This technique is being used to check absorption properties of drug in colon. The relative bioavailability of colonic drug delivery systems can be evaluated by high frequency capsules. Advantages of in this is relative bioavailability from any site of GIT can be evaluated and drug release at various sites of GIT within same object may be used to compare absorption parameters.[7, 18,19]

| Smooth plastic capsule containing small latex balloon, drug and radio-tracer taken orally | → Trigerring system (High frequency generator) | Release of drug and radio tracer trigerred by an impulse. The release is monitored in different parts of GIT by radiological localization |

Table .2- Techniques Employed In Marketed Drugs.

Techniques Employed	Polymers used	Drugs used	Reference
pH dependent	Eudragit L100&S 100	Mesalazine,	20

		Diclofenac sodium&5-ASA	
	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	TRADENAME	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.Olsalazine	Dipentum	5-ASA dimer as capsules and	1g/day	53

		tablets		
7.Sulfasalazine	Salazopyrin	5-ASA linked to sulfapyridine as tablet	1-2g/day	53

Conclusion

Drug delivery to the diseased colon are advantageous in reducing systemic side effects, lower dose of drug, supply of the drug only when it is required and maintainance of the drug in its intact form as close as possible to the target site. Better colonic delivery could be achieved by protecting the drug from absorption and /the environment of the upper GIT and then abruptly released in to proximal colon ,which is the site for colonic targeted delivery of drigs .All the approaches provide means for treatment of local diseases associated with the colon or for systemic absorption of poorly absorbed drugs .The colon is rich in microflora which can be used to target the drug release in the colon.

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