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REVIEW ARTICLE

Colon Targeted Drug Delivery System – A Novel Perspective

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ABSTRACT

In the recent years there is new development in field of colon specific drug delivery system. 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. New systems and technologies have been developed for colon targeting and to overcome pervious method's limitations. Colon targeting holds a great potential and still need more innovative work. This review article discusses introduction of colon, need and approaches of colonic drug delivery, factor effecting colonic transition, colonic diseases and the novel and emerging technologies for colon targeting.

Keywords: Colon targeted drug delivery, delivery of proteins First –pass metabolism, emerging technologies.

INTRODUCTION

Targeted drug delivery to the colon is more desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn‟ s disease, amebiosis, colonic cancer, and systemic delivery of protein and peptide drug. The delivery of drugs to the colon via gastrointestinal (GI) tract requires the protection of a drug from being released in stomach and small intestine. It can be achieved by the use of drug delivery system (DDS) that can protect the drug during its passage to colon. And the drug must be released in the colon from the drug delivery system. Targeting depends on exploiting a unique feature of specific site and protecting the drug until it reaches to the site. Delivery of drugs via colon offers many therapeutic advantages. Drugs, which are destroyed by the stomach acid and metabolized by pancreatic enzymes, are protected. Sustained release of drugs into colon can be useful in the treatment of certain diseases. The colonic delivery is also useful for the systemic absorption of drugs like nifedipine, isosorbide, and theophylline.

The colon is the most suitable site for absorption of peptides and protein drugs for the following reasons:

- less degradation by digestive enzymes,
- proteolytic activity of colon mucosa is less than that observed in small intestine, thus CDDS protect peptide and protein drugs from hydrolysis, and enzymatic degradation in the duodenum and jejunum, and releases the drug into the ileum or colon which produces greater systemic bioavailability.

The colon has a long residence time which is up to 5 days and hence it is highly responsible for enhancement of absorption.The human colon has about 400 different species of bacteria as resident flora, The reactions carried out by this gut flora are azoreduction and enzymatic cleavage i.e. glycosides[1,2].

Anatomy and Physiology of Colon[3, 4]: The large intestine extends from the distal end of the ileum to the anus. Human large intestine is about 1.5 m long. The colon is upper five feet of the large intestine and mainly situated in the abdomen. The colon is a cylindrical tube that is lined by moist, soft pink lining called mucosa; the pathway is called the lumen and is approximately 2-3 inches in diameter. The cecum forms the first part of the colon and leads to the right colon or the ascending colon (just under the liver) followed by the transverse colon, the descending colon, sigmoid colon, rectum and the anal canal (Figure 1). The physiology of the proximal and distal colon differs in several respects that have an effect on drug absorption at

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each site. The physical properties of the luminal content of the colon also change, from liquid in the cecum to semisolid in the distal colon.

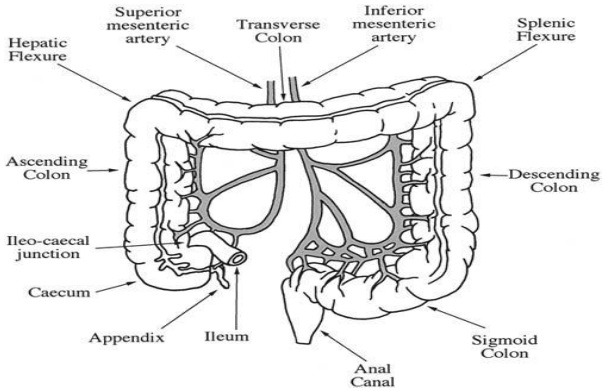

Figure-1.Main feature of the colon

Sr.No.	Large Intestine	Length (cm)
1	Cecum	6-9
2	Ascending colon	20-25
3	Descending colon	10-15
4	Transverse colon	40-45
5	Sigmoid colon	35-40
6	Rectum	12
7	Anal canal	3

Table 1. Length of different parts in colon[4]

pH in the Colon : The pH of the gastrointestinal tract is subject to both inter and intra subject variations. Diet, diseased state and food intake influence the pH of the gastrointestinal fluid. The change in pH along the gastrointestinal tract has been used as a means for targeted colon drug delivery.

Sr.No.	Location	pH
1	**Stomach**	
	Fasted condition	1.5 - 2.0
	Fed condition	3.0 - 5.0
2	**Small intestine**	5.0 - 6.5
	Jejunum	6.0 - 7.5
	Ileum	6.4
3	**Large intestine**	6.7 – 7.3
	Right colon	6.4
	Mid colon & Left colon	6.0 - 7

Table 2- pH of various parts in gastrointestinal tract[4]

There is a pH gradient in the gastrointestinal tract with value ranging from 1.2 in the stomach through 6.6 in the proximal small intestine to a peak of about 7.5 in the distal small intestine (Table 2). The pH difference between the stomach and small intestine has historically been exploited to deliver the drug to the small intestine by way of pH sensitive enteric coatings. There is a fall in pH on the entry into the colon due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides.

Transit of material in the colon: Gastric emptying of dosage forms is highly variable and depends primarily on whether the subject is fed or fasted and on the properties of the dosage form such as size and density. The arrival of an oral dosage form at the colon is determined by the rate of gastric emptying and the small intestinal transit time. The transit times of small oral dosage forms in GIT are given in Table 2. The movement of materials through the colon is slow and tends to be highly variable and influenced by a number of factors such as diet, dietary fiber content, mobility, stress, disease and drugs. In healthy young and adult males, dosage forms such as capsules and tablets pass through the colon in approximately 20-30 hours, although the transit time of a few hours to more than 2 days can occur. Diseases affecting colonic transit have important implications for drug delivery: diarrhea increases colonic transit and constipation decreases it. However, in most disease conditions, transit time appears to remain reasonably constant[5].

Organ	Transit time (hours)
Stomach	1-2
Small intestine	3-4
Large intestine	12

Table 3 Transit time in gastrointestinal tract under normal conditions[5].

Colonic Absorption[6,7]: The surface area of the colon is much less compared to small intestine and is compensated by absence of endogenous digestive enzymes and long residence time of colon (10-24 hours).

Different factors affecting colonic absorption were reported

- Passes through colonocytes (Transcellular transport).
- Passes between adjacent colonocytes (Paracellular transport).

Transcellular absorption involves the passage of drugs through cells and thus the route for most lipophillic drugs takes, where as paracellular absorption involves the transport of drug through the tight junctions between the cells and is the route of most hydrophilic drugs. Drugs shown to be well absorbed include glibenclamide, diclofencac, theophylline, ibuprofen, metoprolol and oxyprenolol. Drugs shown to be less absorbed include furosemide, pyretanide, buflomedil, atenolol

Factors affecting colonic absorption[8]:

- Physical properties of drug such as pKa and degree of ionization.
- Colonic residence time as commanded by GIT motility.
- Degradation by bacterial enzymes and metabolite products.
- Local physiological action of drug.
- Selective and non-selective binding to mucus.
- Disease state.
- Transit through GIT.

Colonic microflora[9,10]: The presence of colonic microflora has formed a basis for the development of colon specific drug delivery system. The human colon is a dynamic and ecologically diverse environment, containing over 400 distinct species of bacteria with a population of 1011 to 1012 CFU/mL, with Bacteroides, Bifidobacterium, Eubacterium, Lactobacillus, etc greatly outnumbering other species. For example, it was reported that Bacteroides, Bifidobacterium and Eubacterium could constitute as much as over 60%of the total cultivable flora. These bacteria produce a wide spectrum of enzymes that, being reductive and hydrolytic in nature, are actively involved in many processes in the colon, such as carbohydrate and protein fermentation, bile acid and steroid transformation, metabolism of xenobiotic substances, as well as the activation and destruction of potential mutagenic metabolites. Nitroreductase, azoreductase, N-oxide and sulfoxide reductase are the most extensively investigated reductive enzymes, while glucosidase and glucronidase are the most extensively studied hydrolytic enzymes. The primary source of nutrition for these anaerobic bacteria is carbohydrates such as non-starch polysaccharides (i.e., dietary fibers) from the intestinal chime. It is well established that non-starch polysaccharides are fermented during transit through the colon and the breakdown in the stomach and small intestine is negligible. Enzymes responsible for the degradation of polysaccharides include α-Larabinofuranosidase, β-D-fucosidase, β-Dgalactosidase, β-Dglucosidase, β-xylosidase, with the last three enzymes being the most active. Additionally, the composition of colonic bacteria and corresponding enzymes can be influenced by many factors, including age, diet, diseases, medication such as antibiotics, and geographic regions. A unique feature of colon microflora is that the growth and activity of certain specific species, most notably bifidobacteria and lactobacilli, can be selectively stimulated by nondigestible oligosaccharides which are known as prebiotics. It has been demonstrated in healthy human volunteers that consumption of fructoolig osaccharides, inulin, lactulose, galactooligosaccharides resulted in a significant increase in numbers of bifidobacteria with or without the decrease in the numbers of bacteroides, clostridium, and fusobacteria in fecal samples.

Advantages[10,11] :

- Reduction in dose size.
- Improve bioavailability.
- Flexibility in design.
- Reduced dose frequency.
- Improved patient compliance.
- Delivery of drug in its intact form as close as possible to the target sites.
- Reduced incidence of adverse side effects improved tolerability.
- Protection of mucosa from irritating drugs.
- Drug loss is prevented by extensive first pass metabolism.
- Lower daily cost to patient due to fewer dosage units are required by the patient.

Disadvantages[10,11] :

- Low dose loading
- Higher need of excipients
- Lack of manufacturing Reproducibility and efficacy
- Multiple formulation steps
- Large number of process variables
- Need of advanced technology.
- Skilled personal needed for Manufacturing of colonic drug delivery system.

Need of colon targeted drug delivery[12,13] :

- Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects.
- Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery.
- Colon-specific drug delivery system is considered to be beneficial in the treatment of colon diseases.
- The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine (targeted).
- A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon.
- Formulations for colonic delivery are also suitable for delivery of drugs which are polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.

Limitations[13,14]:

- As a site for drug delivery, the colon offers a near neutral pH, reduced digestive enzymatic activity, a long transit time and increased responsiveness to absorption enhancers. However, the targeting of drugs to the colon is very complicated.

- Due to its location at the distal portion of the alimentary canal, the colon is particularly difficult to access.
- In addition, the wide range of pH values and different enzymes present throughout the GI tract, through which the dosage form has to travel before reaching the target site, further complicate the reliability and delivery efficiency.
- Successful delivery through this site also requires the drug to be in solution form before it arrives in the colon or, alternatively, it should dissolve in the luminal fluids of the colon, but this can be a limiting factor for poorly soluble drugs as the fluid content in the colon is much lower and it is more viscous than in the upper part of the GI tract.
- The drug could potentially bind in a nonspecific manner to dietary residues, intestinal secretions, mucus or faecal matter. The resident microflora could also affect colonic performance via metabolic degradation of the drug.
- Lower surface area and relative 'tightness' of the tight junctions in the colon can also restrict drug transport across the mucosa and into the systemic circulation.

Criteria for selection of drug for colon drug delivery system (CDDS)[15]

Drug Candidate: Drugs which show poor absorption from the stomach or intestine including peptide are most suitable for CDDS. The drugs used in the treatment of Intestinal Bowel Disease, ulcerative colitis, diarrhea and colon cancer are ideal candidates for local colon delivery. Criteria for selection drugs for CDDS are summarized in table 4.

Drug Carrier: The selection of carrier for particular drug candidate depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. The factors such as chemical nature, stability and partition coefficient of the drug and the type of absorption enhancer chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule. For example, aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond. The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the release properties and efficacy of the systems.

1. **Formation of prodrugs[19,20,21]**:

(Example: Azo- Prodrug, Glucuronide conjugate, etc.) Prodrug is defined as an inert drug that becomes active only after it is transformed or metabolized by the body. Covalent linkage is formed between drug and carrier, which upon oral administration reaches colon without being absorbed from upper part of GIT. In the colon drug release is triggered by high activity of certain enzymes in comparison to stomach and small intestine.

Criteria	Pharmacological class	Non-peptide drugs	Peptide drugs
Drugs used for local effects in colon against GIT diseases	Anti-inflammatory drugs	Oxyprenolol, Metoprolol, Nifedipine	Amylin, Antisense oligonucleotide
Drugs poorly absorbed from upper GIT	Antihypertensive and Antianginal drugs	Ibuprofen, Isosorbides, Theophylline,	Cyclosporine, Desmopressin
Drugs for colon cancer	Antineoplastic drugs	Pseudoephedrine	Epoetin, Glucagon
Drugs that degrade in stomach and small intestine	Peptides and Proteins	Bromophenaramine, 5-Flourouracil, Doxrubicin.	Gonadoreline, Insulin, Interferons
Drugs that undergo extensive first pass metabolism	Nitroglycerin and Corticosteroids	Bleomycin, Nicotine	Protirelin, Sermorelin, Saloatonin
Drugs for targeting	Antiarthritic and Antiasthamatic drugs	Prednisolone, Hydrocortisone, 5-Amino-salicylic acid	Somatropin, Urotoilitin

Table 4. Criteria for selection of drugs for CDDS[15]

Different Approaches For The colon Targeting[17,18] :

a) **Azo bond conjugate**:

Sulfasalazine is mainly used for the treatment of inflammatory bowl diseases. It is 5- Amino Salicylic Acid (5-ASA) prodrug. 85% of oral dose of sulfasalazine reaches to the colon unabsorbed, where it is reduced by the anaerobic environment into 5- ASA and sulphapyridine. Various studies are conducted on sulphapyridine which lead to the formation of other prodrug like Olsalazine, Balsalazine, 4-amino benzoyl-β- alanine. Intestinal microflora produces glycosidase, one of prominent group of enzyme. Colon specific formulation of flurbiprofen had been evaluated by using azo-aromatic and pHsensitive polymer and it was concluded that azoaromatic polymer and pH sensitive polymer eudragit S can successfully be used for colonic drug delivery. Pulsincap drug delivery of salbutamol sulphate had been investigated. An empty gelatin capsule was coated with ethyl cellulose keeping the cap portion as such. A hydrogel plug made of gelatin was suitably coated with cellulose acetate phthalate in such a way that it was fixed to the body under the cap. Eudragit microspheres containing the salbutamol sulphate

were prepared by emulsion solvent evaporation method and were incorporated into this specialized capsule shell. In vitro dissolution results indicated that the onset of drug release was after 7 to 8 hr of the experiment started. Mutual azo prodrug of 5-aminosalicyic acid with histidine was synthesized by coupling L-histidine with salicylic acid, for targeted drug delivery to the inflamed gut tissue

Target sites	Disease conditions	Drug and active agents
Topical action	Inflammatory Bowel Diseases, Irritable bowel disease and Crohn's disease.	Hydrocortisone, Budenoside, Prednisolone, Sulfaselazine, Olsalazine, Mesalazine, Balsalazide.
Local action	Chronic pancreatitis pancreatactomy and cystic fibrosis Colorectal cancer	Digestive enzyme supplements, 5-Flourouracil
Systemic action	To prevent gastric irritation To prevent first pass metabolism of orally ingested drugs Oral delivery of peptides Oral delivery of vaccines	NSAIDS Steroids Insulin Typhoid

Table 5. Colon targeting Diseases, Drugs and Sites[16]

b) **Glucuronide conjugate**:

Glucuronide and sulphate conjugation is the major mechanisms for the inactivation and preparation for clearance of a variety of drugs. Bacteria of the lower gastrointestinal tract secrete glucuronidase that glucouronidate a variety of drugs in the intestine. Since the glucuronidation process results in the release of active drug and enables its reabsorption, glucuronide prodrugs would be expected to be superior for colon targeted drug delivery.

c) **Cyclodextrin conjugates[21]**:

The hydrophilic and ionisable Cyclodextrins can serve as potent drug carriers in the immediate release and delayed release-formulations, while hydrophobic Cyclodextrins can retard the release rate of water. Moreover, the most desirable attribute for the drug carrier is its ability to deliver a drug to a targeted site. Conjugates of a drug with Cyclodextrins can be a versatile means of constructing a new class of colon targeting prodrugs soluble drugs. Ibuprofen prodrugs of α- , β-and γ-Cyclodextrins were investigated. Methotrexate prodrugs of α- and γ-Cyclodextrins were also synthesized and result established the primary aim of masking the ulcerogenic potential of free drug, by using 12-fold dose of the normal dose of methotrexate and equivalent doses of the esters.

d) **Dextran conjugates**:

Dextran ester prodrof metronidazole have been prepared and characterized. Dextran ester prodrugs of dexamethasone and methyl prednisolone was synthesized and proved the efficacy of the prodrugs for delivering drugs to the colon. Methyl prednisolone and dexamethasone wer covalently attached to the dextran by the use of a succinate linker.

e) **Amino-acid conjugates**:

Due to the hydrophilic nature of polar groups like NH2 and COOH, that is present in the proteins and their basic units (i.e. the amino acids), they reduce the membrane permeability of amino acids and proteins. Various prodrugs have been prepared by the conjugation of drug molecules to these polar amino acids. Non-essential amino acids such as tyrosine, glycine, methionine and glutamic acid were conjugated to Salicylic acid.

2. **Hydrogels[22]:**

Hydrogels can be used for site specific delivery of peptide and protein drugs through colon. The Hydrogels are composing of acidic commoners and enzymatically degradable azo aromatic crosslinks. In the acidic pH, gels shows less swelling that protect the drug against degradation in stomach. As the pH of environment increases i.e. become basic, swelling increases. This result is easy access of enzymes like azoreductase, which ultimately release of drug.

3. **Coating with pH dependent polymers[23]**:

The pH in the terminal ileum and colon in higher than in any other region of the gastrointestinal tract and thus dosage forms which disintegrate at high pH ranges can be target into the region. A level of pH is higher in the terminal ileum region then in the cecum. Dosage forms are often delayed at the ileocecal junction, careful selection of enteric coat composition and thickness is needed to ensure that disintegration does not occur until the dosage from moves through the ileocecal junction from the terminal ileum into the cecum. Synonyms for eudragit are Eastacryl, Kollicoat MAE, polymeric methacrylates. Delayed release tablets containing mesalazine and coated with eudragit S-100 were studied. These tablets dissolved at a pH level of 7 or greater, releasing mesalazine in the terminal ileum and beyond for topical inflammatory action in the colon. The formulation was successful in achieving site specific delivery of mesalazine, failure of the coating to dissolve has been reported. The most commonly used pH dependent polymers are derivatives of acrylic acid and cellulose. For colonic drug delivery, drug core is coated with pH sensitive polymers. The drug are includes tablets, capsules, pellets, granules, micro-particles and nanoparticles.

pH- dependent microbeads of theophylline hydrochloride were developed and evaluated by

using alginate and chitosan by ionotropic gelation method followed by enteric coating with eudragit S100. Investigation concentred with the formulation of prednisolone containing 1% eudragit RS PM had been

carried out which shows 100% drug release. Tablet containing mesalazine were investigated which was coated with two polymers eudragit L100 and eudragit S100 in combination 1:0, 4:1, 3:2, 1:1, 1:5, and 0:1. Chitosan microspheres contain Ondansetron were prepared by emulsion cross linking method. Work combines eudragit S100 and chitosan polymers. Analysis regression values suggest that the possible drug release was Peppas model.

Polymer	Threshold pH
Eudragit L-100	6.0
Eudragit S-100	7.0
Eudragit L-30D	5.6
Eudragit FS-30d	6.8
Eudragit L-100-55	5.5
Polyvinyl acetate phthalate	5.0
Hydroxy Propyl Methyl Cellulose Phthalate	4.5-4.8
Hydroxy Propyl Methyl Cellulose Phthalate 50	5.2
HPMC 55	5.4
Cellulose Acetate Trimelliate	4.8
Cellulose Acetate Phthalate	5.0

Table 6: Threshold pH of different polymers suitable for pH dependent drug delivery[24]

4. **Timed released systems[25]**:

(Example: Pulsatile release, Pulsincap, Delayed release, Sigmoidal release system) It is based on the concept of preventing the release of drug 3–5 hr after entering into small intestine. In this approach, drug release from the system after a predetermined lag time according to transit time from mouth to colon. The lag time depends upon the gastric motility and size of the dosage form. One of the earliest approaches is the Pulsincap device. This device consists of a non disintegrating half capsule body sealed at the open end with a hydrogel plug, which is covered by a water-soluble cap. The whole unit is coated with an enteric polymer to avoid the problem of variable gastric emptying. When the capsule enters the small intestine, the enteric coating dissolves and the hydrogel plug starts to swell. The amount of hydrogel is adjusted so that it pops out only after the stipulated period of time to release the contents. In another approach, organic acids were filled into the body of a hard gelatin capsule as a pH-adjusting agent together with the drug substance. The joint of the capsule was sealed using an ethanolic solution of ethylcellulose. The capsule was first coated with an acid soluble cationic polymer, then with a hydrophilic polymer hydroxypropyl methylcellulose and finally enterically coated with hydroxy propyl methyl cellulose acetate succinate. After ingestion of the capsule, the outermost enteric layer of the coating prevents drug release in the stomach. The enteric layer and the hydrophilic layers dissolve quickly after gastric emptying and water starts entering the capsule. When the environmental pH inside the capsule decreases by the dissolution of organic acid, the acid soluble layer dissolves and the enclosed drug is quickly released. Pressurecontrolled drug delivery systems: This approach relies on the strong peristaltic waves in the colon that lead to a temporarily increased luminal pressure. In the upper GIT, the drug delivery system is not directly subjected to the luminal pressure, since sufficient fluid is present in the stomach and small intestine. Due to raised luminal pressure in the colon, the system raptures and releases the drug. Chronomodulated drug delivery system of salbutamol sulphate had been developed for the treatment of nocturnal asthma. The cores containing salbutamol sulphate were prepared by direct compression method use of microcrystalline cellulose and effervescent agent (sodium bicarbonate) and then coated sequentially with an inner swelling layer containing a hydrocolloid (hydroxypropylmethylcellulose E5) and an outer rupturable layer having eudragit RL/RS (1:1). Drug delivery system was investigated which was built on the principles of the combination of pH and time sensitivity. Press- coated mesalamine tablets with a coat of HPMC E-15 were overcoated with eudragit S100.[40] A novel time and pH dependent system was investigated. The system consists of the core tablet of mesalamine which is compression coated with hydroxypropyl methylcellulose (HPMC K4M). This is then coated with eudragit L100. The result revealed that as the amount of HPMC increases, the lag time and t50 value also increases. Osmotic pressure controlled systems: The unit reaches intact to the colon where drug release takes place due to osmotic pressure generated by the entry of the solvent. It is also known as OROS.

5. **Redox sensitive polymer coating** :

Analogues to azo bond cleavage by intestinal enzymes, novel polymers that hydrolyzes nonenzymatically by enzymatically generated flavins are being developed for colon targeting. A common colonic bacterium, Bacteroidesfragilis was used as test organism and the reduction of azo dyes amaranth, Orange II, tartrazine and a model azo compound, 4, 4'- dihydroxyazobenzene were studied. It was found that the azo compounds were reduced at different rates and the rate of reduction could be correlated with the redox potential of the azo compounds.

6. **Bioadhesive systems :**

Bioadhesion is a process by which a dosage form remains in contact with particular organ for an augmented period of time. This longer residence time of drug would have high local concentration or improved absorption characteristics in case of poorly absorbable drugs. This strategy can be applied for the formulation of colonic drug delivery systems. Various polymers including polycarbophils, polyurethanes and polyethylene oxide

polypropyline oxide copolymers have been investigated as materials for bioadhesive systems.

PLATFORM TECHNOLOGIES FOR COLON TARGETED DRUG DELIVERY SYSTEMS[26] :

Nowadays design of dosage form is becoming complex because there is a vast use of technology in the dosage forms for controlling various aspects. Few examples are mentioned in case of colon targeted drug delivery:

PULSINCAP:

Pulsincap was the first formulation developed based on time-release principle. It was similar in appearance to hard gelatin capsule. It consists of water insoluble body water soluble enteric coated cap. The contents are plased with in body plugged wih hydrogel plug. When it is administered, after predetermined time the enteric coat dissolves and the hydrogel plug starts to swell.

CODES:

CODES is a unique colon targeted drug delivery system that was designed to avoid the inherent problems associated with pH or time dependent systems. It consists of core tablets coated with three layers of polymer coatings. The first coating is an acid soluble polymer (Eudragit) and outer layer is enteric with a HPMC barrier layer in between to prevent any possible interaction between the oppositively charged polymers. The core tablet is comprised of the active ingredients and one or more polysaccharides. The polysaccharides are degraded by enterobacteria to generate organic acid. During its transit through GIT, CODES remain intact in the stomach due to enteric protection, but the enteric barrier coating dissolves in the small intestine, where pH is is above 6. Because Eudragit-E starts to dissolves at pH 5; the inner Eudragit-E coating is only slightly permeable and swellable in small intestine. Upon entry into the colon, the bacteria enzymetically degrade the polysaccharide into organic acid.

PORT SYSTEM: It consist of a gelatin capsule coated with a semi-permeable membrane (e.g., cellulose acetate) housing an insoluble plug (e.g., lipidic) and an osmotically active agent along with the drug formulation. When in contact with aqueous medium, water diffuses across the semi-permeable membrane, resulting in increased inner pressure that ejects the plug after a lag time.

OROS SYSTEM:

There are two OROS systems for colon drug delivery:

a. **Osmet pump**:

It consists of an enteric coated semi-permeable shell which encloses an osmotic layer along with a central impermeable and collapsible reservoir filled with drug. The interior of this compartment is connected with the external environment through a delivery orifice at one end. After dissolution of the gastric-resistant film, water is allowed to penetrate through the semi-permeable membrane, thus raising the pressure inside the device. Which cause inner reservoir to shrinks and drug formulation to pump out.

b. **OROS CT**:

Immediately after ingestion, the hard gelatin capsule shell dissolves. The push and pull unit is prevented from absorbing water in the acidic medium of stomach by enteric coating. The osmotic pumping action results when the coating dissolves in the drug is delivered out of the orifice at a rate controlled by the rate of water transport across the membrane.

Alza Corporation developed OROS-CT an osmotically controlled dosage form. It can be used to target the drug locally to the colon for the management of diseases, which are not responding to the systemically absorbed drug. It can be made up of single unit or may incorporate as many as 5-6 push pull units, each with in 4 mm in diameter, encapsulated within hard gelatin capsule. When it reaches to small intestine the enteric coating get dissolved and water enters through the semi-permeable membrane, causing osmogen to swell and the drug compartment gets converted in to flow.

TIME CLOCK SYSTEM :

It consist of a solid dosages form with lipidic barriers containing carnauba-wax and bee-wax along with surfactants, such as polyoxyethylene sorbitan monooleate, In order to prevent the pre mature release of drug in the small intestine the system was further coated with enteric polymers. The release of the drug is independent of the pH and the digestive state of the gut. The release mainly depends upon the thickness of the coat applied. As soon as the coat erodes or emulsifies in the aqueous environment after predetermined lag time, the core gets exposed to the colonic environment resulting in complete release of drug.

CRONOTROPIC SYSTEM :

It consists of a drug containing core coated by hydrophilic swell able HPMC, which is responsible for a lag phase in the onset of release. In, addition, through the application of an outer gastric resistant enteric film, the variability in gastric emptying time can be overcome, and a colon specific drug release can be obtained, relying on the relative reproducibility of small intestinal transit time. The lag time is controlled by the thickness and viscosity grades of HPMC.

TARGIT TECHNOLOGY :

It is based on the application of pH sensitive coating onto injection–molded starch capsules. It is designed for site-specific delivery of drugs to the colonic region. This system has been developed for the treatment of local pathologies of lower GI disease. The clinical data generated has showed its suitability in colon targeted drug delivery.

OPPORTUNITIES IN CDDS[27] :

Targeted delivery to the colon is being explored not only for the local colonic pathologies, thus avoiding the systemic effects of drugs or inconvenient and painful trans colonic administration of drugs, but can be used for systemic delivery of drugs like proteins and peptides, which are otherwise degraded and/or poorly absorbed in stomach and small intestine but can be better absorbed from the colon.

- This is also a potential site for treatment of diseases which are sensitive to circadian rhythms such as asthma, arthritis and angina. Moreover, if there is an urgent need for the delivery of drugs to the colon that is absorbable in the colon, such as steroids, which would increase the efficiency and enable reduce the required effective dose.
- The treatment of disorders of the large intestine, such as irritable bowel syndrome (IBS), Crohn's disease ,colitis, and other colon diseases, where it is necessary to attain a high concentration of the drug, may be efficiently achieved by the colon-specific delivery.
- The development of a dosage form that improves the oral absorption of the peptide and protein drugs whose bioavailability is very low because of the instability in the GI tract is one of the greatest challenges for the oral peptide delivery.
- More research is focused on particular the specificity of drug uptake at the colon site is necessary. These studies would significant in advancing the cause of the colon targeted drug delivery in future

CONCLUSION :

To develop an efficient colon specific acting drug is still a challenge because of its action mainly at colon only. Some of the works done in last two year were really good especially in overcoming the side effects. In future by combining various other strategies, colon targeted drug delivery will find the central place in novel drug delivery.

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