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# A Review on Colon Specific Drug Delivery: Various Approaches Including Novel Approaches and Evaluation

**Dinesh Chandra*[1], Ambikeshwar Pratap Singh[1], Pankaj Kumar Singh[1], Jayant Kumar Maurya[1], Tirthraj[1]**

*1.Kamla Nehru Institute of Management and Technology, Faridipur, Sultanpur, Uttar Pradesh, India*

## ABSTRACT

By name, colonic drug delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e. colon).Targeted drug delivery to the colon would therefore ensure direct treatment at the disease site, lower dosing and fewer systemic side effects. In addition to the local therapy, the colon also can be utilised as a portal for the drugs into the systemic circulation. Colon targeted drug delivery has gained recent importance for the treatment of colonic diseases and systemic delivery of therapeutic proteins and peptides. Treatment could be more effective if it is possible for drug to be directly delivered to colon. This article gives a detailed information related to colon, various approaches current and novel which are employed for delivery of drugs to the colon and advantages and limitation of colonic drug delivery over conventional drug delivery along with evaluation.

**Keywords:** Colon, Target drug delivery.

*Corresponding Author Email: singhambi006@gmail.com

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## INTRODUCTION

The human GI tract is the union of stomach, small intestine and large intestine. Colon is the part of large intestine which starts from the ileocaecal junction to the anus. Colon, rectum and anal canal are the main parts of the large intestine. Colon itself composed of units name caecum, ascending colon, transverse colon, rectum and anal canal. The ascending and descending colon have peritoneal folds which are also called as mesenteries. The histological profile of colon is the longitudinal muscle fibre, submucosal layer, mucous lining one over another. Superior and inferior mesenteric arteries are there for the supply of blood to the colon. A big amount of microflora is present in the colon which plays important role in metabolic undergoing in the intestinal region. The microorganism find colon as a suitable place for their growth. Colon is a storage site of fecal contents and it also has a very high absorption capacity.

Oral route of dosage form administration is the convenient and most commonly used route for colonic drug delivery due to its various advantages it offers in contrast to other routes of drug administration[1].Rectal route of drug administration is also found to be shortest route for targeting drug to colon. Although approaching the proximal part of colon is not easy via rectal route of administration. Rectal administration of drug offers less compliance and is also uncomfortable to the patients[2].

Colonic diseases such as ulcerative colitis, crohns disease, colon cancer, amoebiasis require local therapy and also the systemic delivery of proteins and peptides is achieved by the development of locally acting colon targeted drug delivery system. The proteins and peptides drugs gets inactivated and destroyed in the acidic environment of stomach and in the presence of pancreatic enzyme.

Lymphoid tissue is largely present in the colonic region and thus the mast cell of colonic mucosa produces large amount of antibodies on uptake of antigen, and this results in efficient vaccine delivery[4].Colon has a near neutral pH, longer transit time, proteolytic enzyme activity. The properties of drug, type of delivery system, interaction of drug with healthy, or diseased gut are some of the important factors to be considered for successful colonic drug delivery[3].

Primary approaches used for colon specific drug delivery are pH controlled, time controlled release systems, microbial triggered delivery which include prodrug approach, azo polymeric approach, polysaccharide approach. Novel approaches for colonic drug delivery include pressure controlled drug delivery, CODES,OROS-CT osmotic controlled drug delivery, hydrogels based systems, pressure controlled systems, nanoparticles etc[5].

Oral colon specific drug delivery system has been developed by means of one or more controlled release mechanisms, hardly releases drug in the upper part of GI tract, but rapidly releases drug in the colon following oral administration. The site specificity of the drugs to the target receptor sites has the potential to reduce the side effects and improve the biological response, however for successful colon specific drug delivery, many physiological barriers must be overcome, the major one being the absorption and degradation in the stomach and small intestine, the drug should be absorbed only at the colonic sites.

The bioavailability of poorly soluble drugs in the colonic reasons can be enhanced due to following reasons[5]:

1. This region is recognised as having a somewhat less hostile environment with less diversity and intensity of activity than the stomach and small intestine.
2. Comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus colon drug delivery system protects the peptide drugs from hydrolysis, and enzyme degradation in duodenum and jejunum and eventually releases the drug ileum or colon which leads to greater bioavailability.
3. Colon has a longer residence time which is upto 5 days and is highly responsive to absorption enhancers.

**Need for Colon Targeted Drug Delivery-**

1. For the treatment of various colonic diseases like ulcerative colitis, crohn's disease, colon cancer, irritable bowel syndrome and infections[3].
2. For the treatment of nicotine addition[6].
3. Disease sensitive to circadian rhythms such as asthma, angina and arthritis are treated efficiently by colon targeting of drugs.
4. Delivery of drugs that are found to be absorbable in colon like steroids thereby increasing efficiency and reducing the required effective dose.
5. For the absorption of protein and peptides due to less intensity of digestive and proteolytic enzymes in the colon.
6. Systemic drug delivery to colon results in administration of reduced dose and reduced undesired side effects due to high doses.
7. This site is used for delivery of drugs that undergo degradation in gastric and acidic environment of stomach and irritate gastric mucosa.
8. Required for minimising first metabolism of drugs[4].

**Limitations and challenges in colon targeted drug delivery:**

1. The colon is difficult to access due to its location at the distal portion of alimentary canal.
2. The reliability and delivery efficiency is also doubtful due to presence of wide range of pH values and different enzymes present in the GI tract which is encountered by the drugs before reaching the target site.
3. Colonic contents are considerably viscous because of high water absorption capacity of the colon thereby decreasing the availability of most drugs to absorptive membrane[2].
4. Dissolution could be problem for poorly water soluble drugs because of less free fluid and more viscosity in the colon than in small intestine[3].
5. Drug transport across the mucosa into the systemic circulation is restricted due to lower surface area and relative tightness of tight junction in the colon.

**ADVANTAGES OF COLON DRUG DELIVERY SYSTEM OVER CONVENTIONAL DRUG DELIVERY SYSTEM-**

1.Drugs are directly available at the target site.

2.Comparitively lesser amount of required dose.

3.Improved drug utilisation.

4.Decreased side effects.

**Factors to be considered for colonic drug delivery-**

**Drug candidate-**

1. Drugs which show poor absorption from the stomach and intestine including peptide are most suitable for colon drug delivery.
2. The drug used in treatment of irritable bowel syndrome, inflammatory bowel disease, ulcerative colitis, diarrhoea and colon cancers are ideal candidate for local colon delivery.

**Drug Carrier-**

1. The selection criteria for particular drug candidate depends on the physiochemical nature of the drug as well as the disease state for which is to be used.
2. The factor such as chemical nature, stability, and partition coefficient of drug and the type of absorption enhancers are chosen influence the carrier selection.
3. Moreover the choice of drug carrier depends on the functional groups of drug molecule.

The following points should also be taken in considerations while designing colon specific drug delivery-

1. The physiochemical and biopharmaceutical properties of drugs like solubility and permeability, stability at the intended site of administration should be taken into consideration.

2. The colon specific drug delivery system should be able to control drug release and absorption in the stomach and upper part of GIT and allowing drug release only in colon.
3. The drug needs to be in solution form before it arrives to the colon, where the fluid content is low and viscosity is higher than in upper GIT and making it a limiting factor for poorly soluble drugs.
4. The drug should be released at controlled rate and the released drug should be absorbed from the intestinal lumen without any significant degradation.
5. Developing an appropriate dissolution method for in vitro evaluation of colon targeted system is difficult because of changes in pH across the GIT[4].
6. Various factors such as formulation factors, retention time, retrograde spreading etc influence the concentration of drug reaching the colon.
7. Drug carrier has also a significant role in colon targeted drug delivery.
8. The chemical nature, partition coefficient, stability of drugs are some of the factors to be considered for selection of carrier.
9. Colon targeted drug delivery system are supposed to be delayed release formulations which should be designed either to provide a burst release or sustained release of drug in the colon.

**APPROACHES FOR COLON TARGETTING OF DRUGS-**

**pH dependent approaches-**

The pH dependent system uses the generally accepted view that the pH of the human GIT increases progressively from the stomach(pH 1-2 which increases to 4 during digestion),small intestine (pH 6-7) at the site of digestion and it increases to 7-8 in the distal ileum.

The different pH of the human GIT is exploited by coating the dosage form with pH dependent polymers which remains as such in the upper GIT and degrade in the large intestine where the pH is high(7-8).This approach can be used with any dosage form such as tablet, capsules, pellets etc[23,24].After coating the dosage form with pH sensitive polymers, the active drug is protected from gastric fluid and also a delay in release of drug can be obtained.

As a large variety of polymers are available though by gathering the maximum information of polymers and their solubility at different pH, delivery system are designed to target drug to desired location. Methacrylic acid and methyl methacrylate are most commonly used polymers for colonic delivery of drugs. On the in-vitro evaluation of of eudragit S and Eudragit FS, it was found that Eudragit FS is more appropriate for ileocolonic delivery of drug.

Combination of different polymers, coating level, pH of media are some factors that affect the dissolution rate of eudragit[23].The pH controlled systems are commercially available for some drugs like mesalazine(5 amino salicylic acid),budesonide for the treatment of ulcerative colitis and crohn's disease respectively. The threshold pH of the various enteric coating polymer are depicted below-

**Table 1.Threshold pH of Most Commonly Used Enteric Coated Polymers[7,25,26]-**

| Enteric Polymers | Threshold pH |
|---|---|
| Polyvinyl acetate phthalate | 4.5-5 |
| Cellulose acetate phthalate | 5 |
| Shellac | 7 |
| Eudragit L100 | 6 |
| Eudragit S100 | 7 |
| Eudragit L100-55 | 5.5 |
| Eudragit L 30-D | 5.6 |
| Hydroxyl propyl methyl cellulose phthalate | >5.5 |
| Hydroxyl propyl ethyl cellulose phthalate | 5.2 |
| Cellulose acetate trimelliate | 5.5 |
| Hydroxyl propyl methyl cellulose aceatate succinate | >6 |
| Eudragit FS 30D | 6.8 |

**Table 2.Marketed pH Dependent Systems[7.22]-**

| Drug used | Polymers used | Dosage form | Disease |
|---|---|---|---|
| Tegaserod maleate | Eudragit L100,Eudragit S100 | Tablet | Irritable bowel syndrome |
| Prednisolone | Eudragit L100,Eudragit S100 | Tablet | Ulcerative colitis |

**Embedding in pH sensitive matrices-**

The drug molecules can be embedded in the polymer matrix. Extrusion spheronization technique can be used to prepare uniform size pellets for colon targeted drug delivery. Excipients had a significant impact on the physical characteristics of the pellets. Eudragit S100 as a pH sensitive matrix base in the pellets increase the pellet size and influence pellet roundness.However.eudragitS100 could not cause statistically significant delay in the drug release at lower pH.

**2.Time dependent delivery-**

It is also known as pulsatile release, delayed release or sigmoidal release system. This technique employed delaying the release of the drug until it enters into the colon. Although gastric emptying tends to be highly variable, small intestinal transit time is relatively constant or little bit variation can be observed. The lag time in this technique is mainly considered which is time required to transit from the mouth to colon. A lag time of 5 hours is usually considered sufficient

since small intestine transit is about 3-4 hours, which is relatively constant and hardly affected by the nature of formulation administered. Time controlled systems are useful for delivery of a drug either at preselected times such that patient receives the drug even needed or at a preselected site of GI tract. These systems are therefore particularly useful in the therapy of diseases which depend on the circadian rhythms. This system has some disadvantages which are as follows-

1.Gastric emptying time varies between subjects or in a manner dependent on type and amount of food intake.

2.Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug.

3.Increased in transit rate has been observed in different region of colon has been observed in patients with the inflammatory bowel disease, ulcerative coloitis, diarrhoea, and the carciniod syndrome.

Therefore time dependent systems are not ideal for delivery of drugs to colon specially for the treatment of colon related diseases. Appropriate integration of pH sensitive and time release functions into a single dosage form may improve the site specificity of drug delivery to the colon.

**Pulsincap[8,21]:**

The first formulation introduced based on this principle was pulsincap developed by R.R. Scherer International corporation, Michigan, US .It consists of non disintegrating half capsule body filled with the drug content sealed at the opened end with the hydrogel plug, which is covered by water soluble cap. The whole unit is coated with an enteric polymer to avoid the problems of variable gastric emptying. When the capsule enters the small intestine the enteric coating dissolves and the hydrogel plug start to swell. The length of the plug and its point of insertion control the lag time. For water insoluble drugs a rapid release can be ensured by inclusion of effervescent agents or disintegrants.

The plug material consists of insoluble but permeable and swellable polymers(e.g. polymethacrylates),erodible compressed polymers(e.g. hydroxy propyl methyl cellulose, polyvinyl alcohol, polyethylene oxide),congealed melted polymers(e.g. saturated poly glycolated glycerides, glyceryl monooleate) and enzymatically controlled erodible polymer(e.g. pectin).

Colon specific release can be obtained depending on the relative reproducibility of intestinal transit time. The lag time is controlled by the thickness and the viscosity grades of HPMC. The system is suitable for both capsules and tablets.

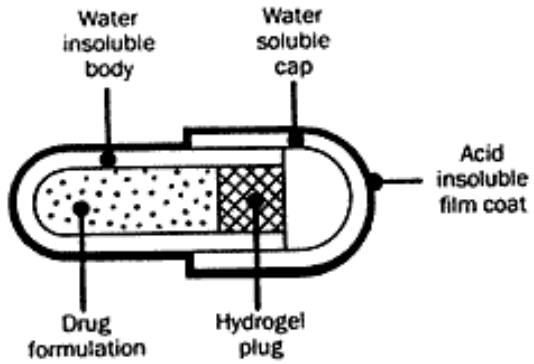


**Figure 1: Design of pulsincap system**

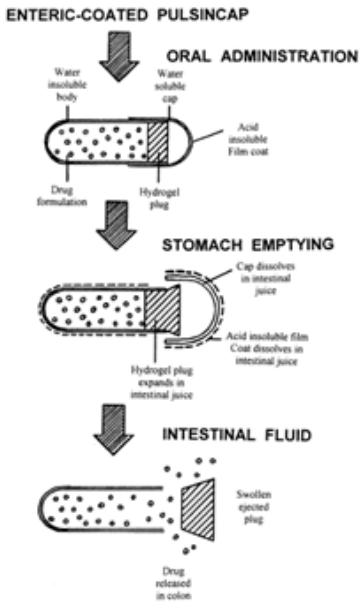


**Figure 2: Enteric coated pulsincap**

**Colon targeted delivery capsule based on pH sensitivity and time release principles[7,8,21]:**

This system contains an organic acid that is filled in a hard gelatin capsule as a pH adjusting agent together with the drug substance. This capsule is then coated with a three layered film consisting of an acid soluble layer, a hydrophilic layer and an enteric layer. After ingestion of the capsule these layers prevent drug release until the environmental pH inside the capsule decreases by dissolution of the organic acid upon which the enclosed drug is quickly released. Therefore the onset time of drug release is controlled by the thickness of acid soluble layer.

**Chronotropic system[21]:**

The chronotropic system consist of a drug containing core coated by hydrophilic sweallable hydroxyl propyl methyl cellulose(HPMC) which is responsible for a lag phase in the onset of release and by applying an outer gastric resistant enteric film ,the variability in gastric emptying can be overcome and a colon specific release can be obtained relying on the relative reproducibility of small intestinal transit time. The lag time is controlled by viscosity and thickness grades of HPMC. The system is suitable both for tablets and capsules.

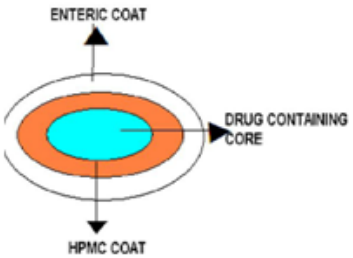


**Figure 3:Design of Chronotropic system**

**PORT system[7,8,21,26]:**

This system consist of a gelatine capsule coated with a semi permeable membrane. Inside the capsule an insoluble plug(lipidic)consisting of osmotically active agent and drug formulation. When in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after a lag time. The lag time is controlled by coating thickness. The system showed good correlation in lag times of *in-vitro* and *in-vivo* experiments in humans. The system proposed to deliver methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHD) in school-age children**.**

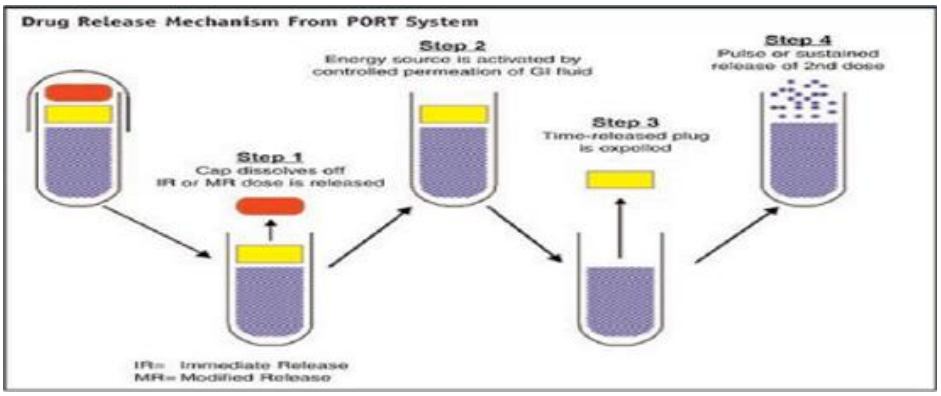


**Figure 4:Design of PORT® system**

**Microbial Triggered Approach:**

The microflora of colon is in the range of $10^{11}$- $10^{12}$CFU/ml[9]. Consisting mainly of anaerobic bacteria eg: bacteroides, bifidobacteria, eubacteria, clostridia, and enterococci.**,** enterobacteria and pnemiococcus etc., thus vast microflora fulfils its energy needs by various types of substrates that have been left undigested in small intestine ex:- di & tri saccharides, polysaccharides etc for this fermentation the microflora, produces a vast number of enzymes like glucoridase, xylosidase, arabinosidase, galactosidase, nucleoreductase,azoreductases, deaminase and urea dehydroxylase, Because of the presence of biodegradable enzymes only in the colon, the use of biodegradable polymers for colon specific drug delivery seems to be more site specific approach as compared to other approaches. These polymer shield the drug from the environment of stomach and small intestine and are able to deliver the drug to the colon on reacting the colon, they undergo assimilation by micro organism as degradation by enzyme as breakdown of polymer back bone leading to subsequent reduction in their molecular weight and thereby loss of mechanical strength.

The principle involved in this system is the degradation of the polymers coated on the dosage form by the microflora of the colon releasing the drug load there [10]. Colon has a range of

complex microflora which fulfils its energy requirements by fermenting the substrate e.g. Polysaccharides present in the intestinal region. These microflora produces wide variety of enzymes which are able to metabolize substrates like carbohydrates and proteins that escape digestion in upper GIT [11,12]. The majority of polymers are used in pharmaceutical composition and generally regarded as safe excipients[2]. Polymer pectin was needed in large quantity when used alone to control the release of drug from the dosage form. But when pectin was mixed with chitosan and hydroxyl propyl methyl cellulose in adequate quantity, it proved to be very efficient to prevent the drug release in stomach and releasing it in the colon Sulphasalazine , a prodrug of mesalazine was the first bacteria sensitive system developed to deliver drug to the colon[13]. The microbially degradable polymers includes Chitosan, Pectins, Guar Gum, Dextrans, Inulin, Lactulose, Amylose, Cyclodextrins, Alginates, Locust bean gum, Chondroitin sulphate, Boswellia gum etc. Microbially triggered approach include the following three approaches mentioned below.

**Prodrug approach:**

Prodrug is defined as the pharmacologically inactive derivative of a parent drug which requires spontaneous or enzymatic transformation *in vivo* in order to release the active agent. In this approach there exist a covalent linkage between the drug and its carrier which remains as such in the upper GIT and breakdown in the colon releasing the drug. A number of linkages of drug with hydrophobic moieties like amino acids, glucoronic acid glucose, galactose, cellulose etc have been prepared which are susceptible to hydrolysis in the colon[5]. The major limitation for prodrug approach is that for its design and development the functional group present on the drug moiety plays a very significant role for chemical linkage . An example of prodrug is 5-ASA, which was conjugated with glycine by amide linkage which was found stable in upper GIT and hydrolysed by ceacal contents to release 5-ASA

**Azo- Polymeric Prodrugs:**

Newer techniques involve the use of different polymers as carrier of drugs for their colonic delivery. Both synthetic as well as naturally occurring polymers are used for this purpose.. Sub synthetic polymers have been used to form polymeric prodrug with azo linkage between the polymer and drug moiety [2]Polymeric prodrug with azo linkage between polymer and drug moiety are designed by using sub synthetic polymers. Polymers cross linked with azo aromatic group when coated on drug protected it from degradation in upper GIT and released in the colon where the azo bonds were reduced. An example of azo polymer based drug delivery system is

segmented polyurethane was coated over the pellets of budesonide and when evaluated in vivo and in vitro resulted in the colonic delivery of drug.

**Polysaccharide based approach:**

Naturally occurring polysaccharides are widely in use for drug targeting because of their abundance, easy availability, and also they are inexpensive. They are highly stable, safe, nontoxic, hydrophilic, gel forming and biodegradable. These include naturally occurring polysaccharides obtained from plant (guar gum, inulin) animal (chitosan, chondrotin sulphate) algal (alginates) or microbial (dextran) origin. These are broken down by the colonic microflora to simple saccharides . So these fall into the category of generally regarded as safe" (GRAS).

**Table 3.Marketted Microbial Controlled System[31,32,33]**

| Drug used | Polymer used | Dosage form | Disease |
|---|---|---|---|
| Valdicoxib | Guar gum and sodium starch glycholate | Tablet | Inflammatory bowel disease |
| 5-flourouracil | Pectin | Tablet | Colon cancer |
| Metranidazole | Sesbania gum | Tablet | Amoebiasis |

**Pressure controlled release system-**

Inside the GIT, contractile and peristaltic movements takes place for the propulsion of intestinal contents. In the large intestine, forcible peristaltic movements called as mass peristalsis occurs which move the intestinal contents from one place to another. These peristaltic waves are of short duration and also they occur only 3 to 4 times a day. In this kind of system the drug is released after the disintegration of water insoluble polymer capsule by the luminal pressure of colon viewed in . The thickness of the membrane is the important factor for the disintegration of the dosage form. The luminal pressure in the colon is higher due to peristaltic motion which in turn is because of viscosity of luminal contents. Takaya et al. (1995) designed the pressure controlled colon specific capsules using ethyl cellulose which is water insoluble[15]. This system also depends on the capsule size. When the pressure controlled capsules were administered to human, a lag time of 3 to 5 hours for drug absorption was noted[11].The capsule shells are made of ethyl cellulose and by controlling the thickness of the shell the collapse time can be controlled. The adequate thickness of capsule wall is about 35-60 micrometers.

**Covalent Linkage of Drug with Carrier[8,21,26,27]**

**Prodrug approaches**:

Prodrug is a pharmacologically inactive derivative of a parent molecule that requires enzymatic transformation in the biological environment to release the active drug at the target site. This approach involves covalent linkage between the drug and its carrier in such a manner that upon

oral administration the moiety remains intact in the stomach and small intestine, and after reached in the colon, enzymatic cleavage regenerate the drug.

**Azo bond conjugate:**

These azo compounds are extensively metabolized by the intestinal bacteria, both by intracellular enzymatic component and extracellular reduction. The use of these azo compounds for colon-targeting has been in the form of hydrogels as a coating material for coating the drug cores and as prodrug. In the latter approach the drug is attached via an azo bond to a carrier. This azo bond is stable in the upper GIT and is cleaved in the colon by the azo-reductases produced by the microflora.

**Glycoside conjugation:**

Steroid glycosides and the unique glycosidase activity of the colonic microflora form the basis of a new colon targeted drug delivery system. Certain drugs can be conjugated to different sugar moieties to form glycosides. The drug part forms the aglycone and is linked to the sugar part, which forms the glycone part of the glycoside. Because they are bulky and hydrophilic, these glycosides do not penetrate the biological membranes upon ingestion. They breakdown upon action of glycosidase, releasing the drug part from the sugar. The presence of glycosidase activity in the small intestine could pose a problem in delivery of these conjugates to the large bowel, because some hydrolysis of the conjugate can be expected in the small intestine. However, the small intestinal transit time, when compared to the large intestinal transit time, is short, and moreover, considering the time required for the hydrolysis of glycosidic bond, these conjugates can be expected to be good colon specific drug carriers. The major glycosidase enzymes produced by the intestinal microflora are β -D-galactosidase, α -L-arabinofuranosidase, β -D-xylopyranosidase, and β –Dglucosidase. These glycosidase enzymes are located at the brush border and hence are accessible to substrate easily.Example: lucosides, galactosides, and cellobiosides of dexamethasone, prednisolone, hydrocortisone, and fludrocortisone. Daxamethasone-21-β-glucoside, Prednisolone-21-β-glucoside.

**Glucoronide conjugates**:

Bacteria of the lower GIT secrete b-glucuronidase and can deglucuronidate a variety of drugs in the intestine. Thus, the deglucuronidation process results in the release of the active drug again and enables its reabsorption. Example: Opiates, when taken for the relief of pain, cause severe constipation by inhibiting GIT motility and secretions. Narcotic antagonists, when given as antidotes for GIT side effects, immediately relieve constipation but precipitate acute withdrawal. This is because these narcotic antagonists are not selective and they not only affect the GIT

activity, but also the central nervous system (CNS). A novel approach would be to target these antagonists to the lower bowel so that they are not absorbed systemically. With this purpose, naloxone and nalmefene glucuronide prodrugs were prepared to target these drugs to the colon. When given orally to morphine dependent rats these prodrugs showed increased GIT motility and secretion in the large bowel results in a diarrhea and The resultant diarrheal flushed out the drug/prodrug from the colon thereby preventing the

systemic absorption of the antagonist, which in-turn caused absence of withdrawal symptoms. Budesonide-b-glucuronide prodrug also found to be superior to budesonide itself for the treatment of colitis in the rat.

**Cyclodextrin conjugate:**

Cyclodextrins are cyclic oligosaccharides consisted of six to eight glucose units through -1,4 glucosidic bonds and have been utilized to improve certain properties of drugs such as solubility, stability and bioavailability. The interior of these molecules is relatively lipophilic and the exterior relatively hydrophilic, they tend to form inclusion complexes with various drug molecules. They are known to be rarely capable of being hydrolyzed and only slightly absorbed in passage through the stomach and small intestine however, Colonic bacteria are capable of degrading cyclodextrins for carbon source by stimulating cyclodextranase activity. They are fermented by the colonic microflora to form small saccharides that are then absorbed. This susceptibility to degradation specifically by colonic micro flora together with their property to form inclusion complexes with various drugs makes them particularly useful in carrying drug moieties to the colon.

**Dextran conjugate:**

Dextrans are polysaccharides of bacterial origin where the monosaccharides are joined to each other by glycoside linkages. These linkages are hydrolyzed by moulds, bacteria, and mammalian cells. The enzyme responsible for the hydrolysis of these linkages is dextranase. The dextranase activity is almost absent in the upper GIT, where as high dextranase activity is shown by anaerobic gram-negative bacteria, especially the Bacteroides, which are present in a concentration as high as $10^{11}$ per gram in colon. This led to the use of dextran as carriers for drug molecules to the colon. In the colon, dextran's glycosidic bonds are hydrolyzed by dextranases to give shorter prodrug oligomers, which are further split by the colonic esterases to release the drug free in the lumen of the colon. Dextran prodrug approach can be used for colon-specific delivery of drugs containing a carboxylic acid function (−COOH).NSAIDS ware directly coupled to dextran by using carboxylic groups of drugs. Example is Naproxen-dextran conjugate.

Glucocorticoids do not possess −COOH group so these are linked to dextran using spacer molecule. e.g. glucocorticoid-dextran conjugates.

**Amino acid conjugation:**

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. Increase in hydrophilicity and chain length of carrier amino acid; decrease the permeability of amino acids and proteins. So the amino acid conjugate show more enzymatic specificity for hydrolysis by colonic enzyme.

**Polymeric prodrugs:**

Newer approaches are aimed at use of polymers as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers are used for this purpose. Sub-synthetic polymers have used to form polymeric prodrug with azo linkage between the polymer and drug moiety

**Novel approaches-**

**TARGIT Technology**:

This technology is developed for the targeted delivery of drugs in colonic region. It is mainly used in the delivery of therapeutic agents to the lower GIT for local treatment of disorders. In this technique pH sensitive coating is done on the moulded starch capsules. The in vivo studies confirmed that about 90% of the TARGIT Capsules delivered their contents to the target site [16].TARGIT based product are in active clinical development for the treatment of conditions including inflammatory bowel diseases.

**Nanoparticles for Colon Targeted Drug Delivery**[7,21,27]:

Nanoparticles are now a days become novel area for colon specific drug delivery . These are novel approaches used to target drugs. These are small colloidal particles of size about 200 nm made up of biodegradable and non- biodegradable polymers. The drug moiety can be dissolved, entrapped, or encapsulated in the nanoparticle matrix. They are better than conventional dosage forms in many aspects .They results in more efficacy, reduced toxicity, better bio-distribution and improved patient compliance. They results in controlled release due to biodegradability, pH, ion, temperature sensitivity.

**COLAL-PRED system**[8,21]:

This system is designed by Alizyme for the treatment of ulcerative colitis. It is the combination of Alizyme's colonic delivery system, COLAL, and an approved generic steroid, Prednisolon sodium metasulfobenzoate. It provides the effective treatment of ulcerative colitis without the

side effects of steroids. There is no competitor of this product yet in the market. Its colon targeting is done by coating it with such substances which get degraded by the colonic bacteria[17].

**Hydrogels Based Approach[8,26,27]:**

Hydrogels may be defined as the 3-D polymer network which is hydrophilic in nature and because of which it is able to swell in water or other biological fluids. It has the ability to retain a significant amount of fluid in the swollen state. The property of water absorption of hydrogels is due to the presence of hydrophilic groups such as OH-, -CONH-, -COOH etc. The hydrogels are used as delivery systems because of their ability to allow the passage of drug across its structure. The mechanism of drug release in this kind of systems is diffusion because hydrogels have good permeability for water soluble drugs. Hydrogels can be formulated in a number of physical forms like microparticles, coating, films, nanoparticles.

The commonly used hydrophilic polymers for hydrogels are PEG, PVA, PAA, Polymethacrylic acid, Polyacrylamide[18]. These polymers can absorb water from a fraction to several thousand of their own weight . Diffusion controlled release is the considered the primary method of drug release from dosage form. The mesh size of hydrogels range from 5-100 nm which is much larger than the most drugs. In some cases diffusion of drugs is faster than the hydrogel distension, then swelling is considered the limiting factor for drug release and these systems are called as Swelling controlled systems . These can be further divided on the basis of the type of chemical reaction occurring during drug release. Various stimuli sensitive hydrogels like pH, temperature sensitive hydrogels are prepared to target drugs or proteins to colon and other therapeutic agents to tumors[19].

**Table 4.Marketted Hydrogels System[7]-**

| Drug used | Polymer used | Approach used | Method of preparation |
|---|---|---|---|
| Satranidazole | Chitosan | pH sensitive | Cross linking method |
| 5-fluorouracil | Hydroxyethylmethacrylate, Methacryloyloxy azobenzene | Degradation by Azoreductase | polymerisation |

**Gas Empowered Drug Delivery System (GEDD)**:

It is also a novel drug delivery system to colon which is designed to target the proteins and peptides to the intestinal region by using mucoadhesive polymer polyethylene oxide and TMC as penetration enhancer using $CO_2$. By the presence of mucoadhesive polymer the drug remains adhered to the mucous layer and the permeation enhancer is used to open the tight junctions to promote paracellular pathway for drug absorption. In this system the $CO_2$ gas is used as driving

force to push the drug substance to the absorbing membrane and also it covers the dosage form completely to protect it from enzymatic and proteolytic degradation.$CO_2$ also functions as permeation enhancer by opening the tight junctions mechanically. This system is successful in delivering the drug to the intestine because of the use of cellulose acetate phthalate which protects the dosage form from the acidic pH of stomach 80

**Microspheres[8,28]:**

Microspheres are used now a days for the delivery of proteins and peptides .They provide stability to the compounds which are prone to degradation in vivo. The microspheres shield the drug from the acidic environment of stomach and target the drug to the desired site, and also improve drug absorption from paracellular route . The mechanisms of drug release from microspheres can be diffusion, degradation, hydrolysis or erosion . The drug encapsulated in microspheres have shown increased stability, reduced toxicity and also targeted delivery to the site of action. Example theophylline microspheres prepared by ionotropic gelation method using Ca-pectinate and Eudragit S100 for anti asthamatic activity.

**Osmotic controlled drug delivery[7,8,21]:**

The OROS-CT system can be single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4mm in diameter, encapsulated within a hard gelatin capsule. Each push-pull unit is bilayer laminated structure containing an osmotic push layer and a drug layer, both surrounded by a semi-permeable membrane. In principle semi-permeable membrane is permeable to the inward entry of water and aqueous gi fluids and is impermeable to the outward exit of the drug. An orifice is drilled into the semi-permeable membrane to the drug layer. The outside surface of the semi-permeable membrane is then coated by eudragit®S100 to delay the drug release from the device during its transit through the stomach. Upon arrival on the small intestine the coating dissolves at pH≤7. As a result water enters the unit causing the osmotic push compartment to swell forcing the drug out of the orifice into colon. For treating ulcerative colitis, each push pull unit is designed with a 3-4 hour post gastric delay to prevent drug delivery in the small intestine. Drug release begins when the unit reaches the colon. OROS-CT units can maintain a constant release rate for up to 24 h in the colon.

**Novel Colon Targeted Delivery System (CODESTM)[7,8,21,26]**

CODESTM is a unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems. CODESTM is a combined approach of pH dependent and microbial triggered CDDS. It has been developed by utilizing a unique mechanism involving lactulose, which acts as a trigger for site specific drug release in the colon.

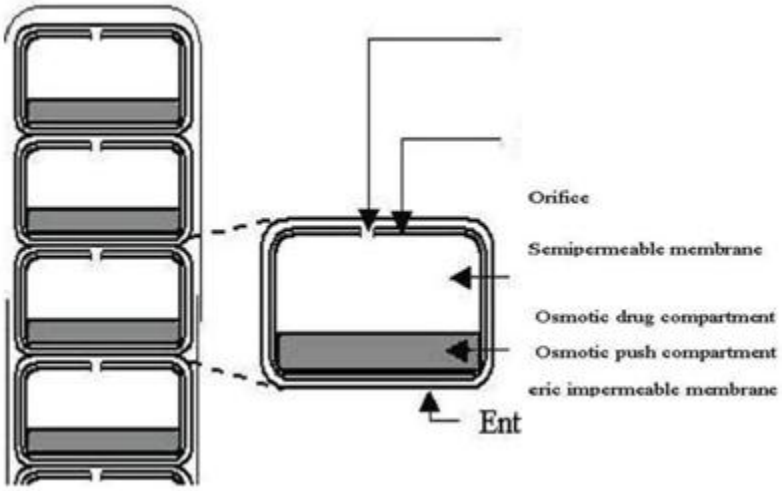


**Figure 5: Cross section of OROS-CT colon targeted drug delivery system**

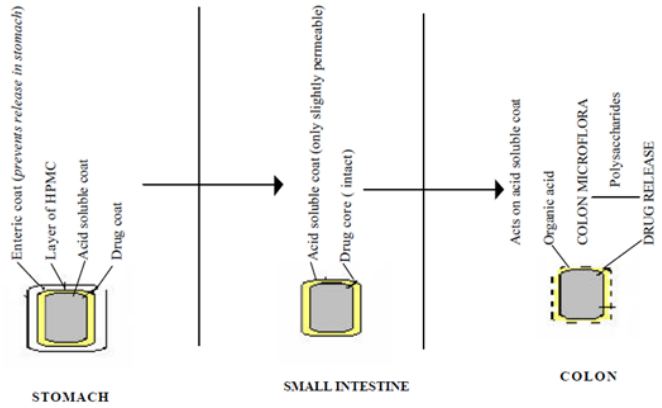


**Figure 6: Schematics of the conceptual design of CODES™**

The system consists of a traditional tablet core containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently over coated with an enteric material, Eudragit L. The premise of the technology is that the enteric coating protects the tablet while it is located in the stomach and then dissolves quickly following gastric emptying. The acid soluble material coating then protects the preparation as it passes through the alkaline pH of the small intestine. Once the tablet arrives in the colon, the bacteria enzymatically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH surrounding the system sufficient to effect the dissolution of the acid soluble coating and subsequent drug release.

**Ticking capsule[21]:**

It is a chronotherapeutic devices employ some electrical means of controlling pulsatile drug release coupled with electronic timing. Ticking capsules is divided into three compartments: Porous Si-based drug delivery module, Electronic control module (e.g. mucontroller) and Battery. Many human illnesses and their symptoms show a regular (rhythmic) pattern:

Hypertension (early morning); arthritics pain (mid afternoon); heart attack (early morning + late afternoon and asthma attack (night). It is recognizing intake into the body is limed to match the severity of the Symptom.

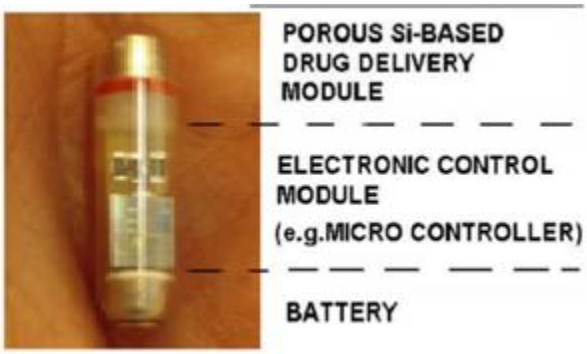


**Figure 7:Design of Ticking capsule system**

**Enterion capsule Technology**[21,26,27]

The Enterion capsule has recently been developed by Phacton Research, Nottingham, UK, for targeted delivery of a wide range of different drug formulations into any region of the gut (Fig). It is a 32-mm long, round-ended capsule and contains a drug reservoir with a volume capacity of approximately 1 ml. The capsule can be loaded with either a liquid formulation (e.g. Solution, Suspension) or a particulate formulation (e.g., powder, pellets, in sit affects etc.) through an opening 9 mm in diameter, which is then sealed by inserting a push-on Cap fitted with a silicone O-ring. The floor of the drug reservoir is the piston face, which is held back against a compressed spring by a high tensile strength polymer filament.

**Figure 8:Design of Enterion capsule**

A radioactive marker is placed inside a separate sealed tracer port to allow real time visualization of the capsule location using the imaging technique of gamma Scintigraphy. When the capsule reaches the target location in the gastrointestinal tract, the contents are actively ejected by the external application of an oscillating magnetic field. The frequency of the magnetic field is set in

the low MHz region, low enough so that there is negligible absorption of the energy by the body tissues but sufficiently high enough to induce unable power in a tuned coil antenna embedded in the capsule wall. The power induced in the coil by the magnetic field is fed to a tiny heater resistor located within a separate sealed electronics compartment inside the capsule. Although the power is only a few tenths of a wall, the small size of the heater (less than 1mm3) means that heat build up is extremely rapid. The heater resistor is in direct contact with the restraining filament, causing it to softer and breaks with the increase in temperature. This is turn, releases the spring and driver the piston. The resulting increase in pressure within the drug reservoir forces off the O-ring sealed cap and rapidly ejects the drug or drug formulation into the surrounding GI fluids. The piston motion is stopped near the end of the capsule, which maintains a seal and presents contact of the internal electronic compartments with the GI fluids. The movement of the piston also operates a switch, which directs some of the electrical energy away from the heater and uses it to transmit a weak radio signal at a precise frequency. Detection of this signal externally confirms that the capsule has opened successfully.

**Evaluation techniques of Colon Targeted preparations[7,8,21]:**

***In Vivo* Evaluation**

A number of animals such as dogs, guinea pigs, rats and pigs are used to evaluate the delivery of drug to colon because they resemble the anatomic and physiological conditions as well as the microflora of human GIT. While choosing a model for testing a CDDS, relative model for the colonic diseases should also be considered. Eg. Guinea pigs are commonly used for experimental IBD model. The distribution of azoreductase and glucouronidase activity in the GIT of rat and rabbit is fairly comparable to that in the human. For rapid evaluation of CDDS a novel model has been proposed. In this model the human fetal bowel is transplanted into a subcutaneous tullel on the back of thymic nude mice, which vascularizes within 4 weeks, matures and becomes capable of developing of mucosal immune system from the host.

**Clinical Evaluation**

Absorption of drugs from the colon is monitored by colonoscopy and intubation. Currently gamma scintigraphy and high frequency capsules are the most preferred techniques employed to evaluate colon drug delivery systems.

**High frequency capsule:**

Smooth plastic capsule containing small latex balloon, drug and radiotracer taken orally. Triggering system is high frequency generator. Release of drug & radiotracer triggered by an

impulse, the release is monitored in different parts of GIT by radiological localization. It checks the absorption properties of drug in colon[29].

**Gammascintigraphy:**

By means of gamma scintigraphic imaging, information can be obtained regarding time of arrival of a colon-specific drug delivery system in the colon, times of transit through the stomach and small intestine, and disintegration. Information about the spreading or dispersion of a formulation and the site at which release from it takes place can also be obtained. Gamma scintigraphic studies can also provide information about regional permeability in the colon. Information about gastrointestinal transit and the release behaviour of dosage forms can be obtained by combining pharmacokinetic studies [30].

**X-ray imaging:**

The dogs were used for the in vivo evaluation of dosage form by x ray method.50 ml of radiodiagnostic agent, omnipaque was given to the dogs. Then after specific time intervals post administration of omnipaque x-ray imaging was done. This was done to get reference dog GIT x-ray images for comparison. During x-ray imaging the animals are subjected to fast overnight with full access to water and a radiograph is made before the administration of the substance under test. Then the units are administered along with 50 ml of water. The radiograph of animals were taken at 0hr,0.5hr,2.5hr,4hr,5hr,6hr,7hr,8hr after the ingestion of substance under test[16].

**In vitro evaluation[7,8]:**

*In vitro* evaluation techniques involves the simulation of the in vivo conditions of the GIT, like pH, volume, bacteria, enzymes food particles etc under the laboratory conditions. The conventional basket method is usually used for performing the in vitro dissolution studies of a dosage form. The dissolution studies are carried out in different buffer solutions to mimic the GIT environment and to know the behaviour of dosage form under different pH conditions. The in vitro tests for enteric coated systems is done by keeping them in simulated stomach pH conditions (0.1 N HCl) for 2 hrs (mean gastric emptying time) and then in the simulated intestinal pH conditions for next 3 hrs (mean small intestine transit time). The site and amount of degradation and dissolution of the dosage form is thus predicted during the *in vitro* studies .

***In vitro* enzymatic test[8]:**

For this there are 2 tests:

1. Incubate carrier drug system in fermenter containing suitable medium for bacteria (*Streptococcus faccium* or *B.ovatus*) amount of drug released at different time intervals is determined.

2. Drug release study is done in buffer medium containing enzymes (enzyme pectinase, dextranase), or rat or guinea pig or rabbit cecal contents. The amount of drug released in particular time is determined, which is directly proportional to the rate of degradation of polymer carrier.

## CONCLUSION-

The colonic region has gained recent importance as an important site for drug delivery and absorption. Colonic drug delivery system offers considerable benefits to patient in term of both local and systemic treatment. The most important task for delivery of drug to the colon is to prevent or inhibit the release of the drug in the upper part of gastrointestinal tract and release in the colon. Due to limitations of various approaches researchers have invented various novel approaches which are able to release the drug in the colon and thats why minimising limitations of various old approaches i.e reduced side effects, lower dose of drug is required and supplying drug to target site. Several approaches have been investigated to achieve site specify of drugs. Novel approaches like CODES$^{TM}$,OROS-CT ,nanoparticulates system etc showed significant potential in this area. These recent advances in colonic drug delivery system have promoted targeting of drugs, proteins and peptides in treatment of various colonic diseases.

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