Review on Recent and Novel Approaches to Colon Targeted Drug Delivery Systems

Keywords: Colon targeted drug delivery system, Prodrug, pH and time dependent systems and microbial triggered systems

ABSTRACT

This article focuses on the potential opportunities and challenges available in new area of colon targeted drug delivery system. Colon is a site where both local and systemic delivery of drugs can take place and oral administration of different dosage forms is the most common form of administration due to greater patient compliance and flexibility. Colon targeted drug delivery system is used for the treatment of various diseases related to colon like inflammatory bowel disease, Crohn’s disease, colon cancer, etc. Colonic drug delivery has gained importance not just for the delivery of the drugs in the treatment of local diseases associated with it but also for the systemic delivery of proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs and anti-diabetic agents. In this review the various concepts and approaches including prodrug, pH and time dependent systems and microbial triggered systems used in the development of colon specific drug delivery are discussed. Review also focuses on the novel approaches namely pressure controlled colonic delivery, osmotic controlled drug delivery and CODESTM.

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INTRODUCTION

Colon specific drug delivery has gained a more importance in delivery of the drug in colonic region by use of various drugs to treat the both local and systemic diseases. Local diseases include Crohn’s disease, ulcerative colitis, and colorectal cancer and other serious disorders like nocturnal asthma, hypertension, arthritis and angina can also be cured by these techniques. Colonic delivery is a good candidature for delivery of proteins peptides and vaccines where the enzymatic degradation and the hydrolysis of proteins can be minimized and increases the systemic bioavailability. During the past decades research is going on to develop the methods to target the drug to the specific region. The goal of targeted drug delivery is to deliver the drug to the specific organ. Drug delivery to the colon is beneficial not only for the oral delivery of proteins and peptide drugs (degraded by digestive enzymes of stomach and small intestine) but also for the delivery of low molecular weight compounds used to treat diseases associated with the colon or large intestine.

Table No. 01: Colonic diseases, its sites and active drug components

<table>
<thead>
<tr>
<th>Targeted Site</th>
<th>Diseases</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>Colorectal cancer, Cystic fibrosis, Chronic pancreatitis, Pancreatostomy</td>
<td>5- fluorouracil, Digestive enzymes</td>
</tr>
<tr>
<td>Systemic</td>
<td>Oral delivery of vaccines, To prevent gastric irritation, To prevent first pass metabolism of orally administered drugs Oral delivery of peptides</td>
<td>Typhoid, NSAIDS, Steroids, Insulin</td>
</tr>
<tr>
<td>Topical</td>
<td>Inflammatory bowel diseases (Crohn’s disease, Ulcerative colitis), Irritable bowel Diseases, Amoebiasis</td>
<td>Hydrocortisone, Prednisolone, Sulfasalazine, Mesalazine, Mercaptopurine, Metronidazole, Tinidazole, mebendazole</td>
</tr>
</tbody>
</table>
Anatomy and Physiology of Colon

Fig. No. 01 Anatomy of colon

The GIT measures about 5 meters long. The different parts of GIT are divided into upper and lower gastrointestinal tract. The upper GIT includes oesophagus, stomach, and duodenum. The lower GIT includes small intestine and large intestine. The small intestine measures an average of about 6.9 meters to 7.1 meters. It includes duodenum, jejunum and ileum. The main function of small intestine is the absorption of nutrients and minerals from food. The retention time of small intestine is 3-5 hr. The large intestine extending from the ileocecal junction to the anus is divided in to three main parts i.e. colon, the rectum and anal canal. The entire colon is about 5 feet (150 cm) long, and is divided in to five major segments. Peritoneal folds called as mesentery which is supported by ascending and descending colon. The right colon consists of the cecum, ascending colon, hepatic flexure and the right half of the transverse colon. The left colon contain the left half of the transverse colon, descending colon, splenic flexure and sigmoid. The rectum is the last anatomic.

The colon is having high water absorption capacity, the colonic contents are considerably viscous and their mixing is not efficient, thus availability of most drugs to the absorptive membrane is low. The human colon has over 400 distinct species of bacteria as resident flora, a possible population of up to 1010 bacteria per gram of colonic contents. The major function of the colon is the creation of suitable environment for the growth of colonic microorganisms,
storage reservoir of faecal contents, expulsion of the contents of the colon at an appropriate time and absorption of potassium and water from the lumen. The absorptive which more than 90% of the fluid is absorbed. Among the reactions carried out by these gut flora capacity is very high, each about 2000 ml of fluid enters the colon through the ileocecal valve are azoreduction and enzymatic cleavage i.e. glycosides. These metabolic processes may be responsible for the metabolism of many drugs and may also be applied to colon targeted delivery of peptide based macromolecules such as insulin by oral administration.

**Need to target a drug in colonic region:**

The drug targeted to colon will ensure following points,

- Direct treatment at the disease site, lower dosing and fewer systemic side effects.
- Allow oral administration of peptide and protein drugs.
- Colon-specific formulation could also be used to prolong the drug delivery.
- Both local and 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).
- 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.
- 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.

**General considerations for designing of colon specific formulations:**

To achieve a desired therapeutic action of dosage form, it is necessary to design a suitable formulation with suitable qualities. In general, delayed release dosage forms are designed to provide a burst release or a sustained/ prolonged release once they reach colon.

Various included factors are:

- Pathology and pattern of diseases, especially the affected parts of lower GIT or, Physiology and physiological composition of the healthy colon if the formulation is not intended for
localized treatment.

- Physicochemical properties and biopharmaceutical properties of the drug such as solubility, stability and permeability at the intended site of delivery, and the desired release profile of the active ingredient.

Formulation of drugs for colon specific delivery requires careful consideration of dissolution of and/or release rate in the colon fluids. Due to the presence of less fluid content in large intestine than in small intestine the dissolution and release rate from the formulations decreases. The poor dissolution and release rate may in turn lead to lower systemic availability of drugs. These issues could be more problematic when the drug candidate is poorly water soluble and/or require higher doses for therapy. Consequently, such drugs need to be delivered in pre-solubilised form, or formulation should be targeted for proximal colon, which has more fluid than in the distal colon. Aside from drug solubility, the stability of the drug in the colonic environment is a further factor that warrants attention. The drug could bind in a nonspecific manner to dietary residues, intestinal secretions, mucus or general faecal matter, thereby reducing the concentration of free drug. Moreover, the resident micro-flora could also affect colonic performance via degradation of the drug.

Factors affecting colon targeting:

Several factors will affect colon targeting which generally include physiological factors and pharmaceutical factors.

Physiological factors:

It generally includes Gastric emptying, pH of colon and Colonic micro flora and enzymes.

Gastric emptying:

Drug targeting to the colon upon oral administration depends mainly on gastric emptying and bowel transit time. Upon reaching the colon the transit time of dosage form depends on the size of the particles. Smaller particles have more transit time compared to larger particles. Diarrhoea patients have shorter transit time whereas constipation patients have longer transit times.
Table No. 02: Measurements of Parts of GIT and its transit time.

<table>
<thead>
<tr>
<th>GI Organs</th>
<th>Measurements (Length)</th>
<th>Small Intestine</th>
<th>Large Intestine</th>
<th>Rectum</th>
<th>Anal Colon</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total length 03 meter</td>
<td>Total length 1.5 meter</td>
<td>20cm</td>
<td>03cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Duodenum: 25cm</td>
<td>-Cecum: 0 6 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Jejunum: 01m</td>
<td>-Colon:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Ileum: 02m</td>
<td>-Ascending colon: 20-25cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Transverse colon: 10-15cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Descending colon: 40-45cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transit through</td>
<td></td>
<td>Fasted state</td>
<td>Fed state</td>
<td>Small intestine transit</td>
<td>Colon transit</td>
</tr>
<tr>
<td>Time</td>
<td></td>
<td>10 min to 02 hrs</td>
<td>Greater than 02 hrs</td>
<td>03 to 04 hrs</td>
<td>20 to 35 hrs</td>
</tr>
</tbody>
</table>

**pH of colon:**

The pH of GIT varies between different individuals. The food intakes, diseased state etc. influences the pH of the GIT. This change in the pH in different parts of GIT is the basis for the development of colon targeted drug delivery systems. Coating with different polymers is done to target the drug site.

Table No. 03: pH of different parts of GIT

<table>
<thead>
<tr>
<th>Parts of GIT</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td></td>
</tr>
<tr>
<td>Fasted state</td>
<td>1.5-2</td>
</tr>
<tr>
<td>Fed State</td>
<td>2-6</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>6.6-7.5</td>
</tr>
<tr>
<td>Colon</td>
<td></td>
</tr>
<tr>
<td>Ascending colon</td>
<td>6.4</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>6.6</td>
</tr>
<tr>
<td>Descending colon</td>
<td>07</td>
</tr>
</tbody>
</table>

Colonic micro flora and enzymes:

The GIT contains a variety of microorganisms that produces many enzymes need for metabolism. Growth of this micro flora is controlled by the GIT contents and peristaltic movements. The enzymes released by different microorganisms E. coli, Clostridia, Lactobacilli, Eubacteria, Streptococci are responsible for the various metabolic reactions that take place in the GIT.

Table No. 04: Different micro flora, enzymes and its metabolic reactions

<table>
<thead>
<tr>
<th>Micro flora</th>
<th>Enzymes</th>
<th>Metabolic reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em>, Bacteroids</td>
<td>Nitroreductase</td>
<td>Reduces compounds aromatic &amp; heterocyclic nitro</td>
</tr>
<tr>
<td>Clostridia, Lactobacilli</td>
<td>Hydrogenase</td>
<td>Reduces carbonyl groups &amp; aliphatic double bonds</td>
</tr>
<tr>
<td>Clostridia, Eubacteria</td>
<td>Glucosidase</td>
<td>Cleavage of glycosidase of alcohols &amp; phenols</td>
</tr>
<tr>
<td>Eubacteria, Clostridia, Streptococci</td>
<td>Sulfatase</td>
<td>Cleavage of Osulphates &amp; sulfamates</td>
</tr>
</tbody>
</table>

Pharmaceutical Factors:

Drug candidates:

Due to high retention time of colon, colon causes an increase in the absorption of poorly absorbed agents like peptides, etc. drugs used for treatment of inflammatory bowel diseases, etc. are suitable for colon targeted drug delivery system.

Drug carriers:

The selection of carrier for CDDS depends on the nature of the drug, disease for which the drug is used. The various physicochemical factors of drug that effect the carrier selection includes chemical nature, stability, partition coefficient, functional groups of drug molecule, etc.
Polymers Used in Colon Targeting:
Polymer contains a large number of structural unit joined by same type linkage, form into a chain like structure. These are nowadays used in formulating various pharmaceutical products. Naturally found polymer, which include gummy exudates, proteins, enzymes, muscle fibre, polysaccharides. In olden days natural polymers are widely used in pharmacy but a variety of synthetic polymer are used nowadays for pharmaceutical and cosmetic development, using these polymer many therapeutic system of body namely controlled drug delivery systems, are achieved.

Natural polymer:
Guar gum, Pectin, Cyclodextrin, Dextran, Amylase, Chitosan, Chondrotin sulphate, Locust bean gum.

Synthetic polymer:
Shellac, Ethyl cellulose, Cellulose acetate phthalate, Hydroxy propyl methyl cellulose, Eudragit, Polyvinyl acetate phthalate.

Approaches for Site Specific Drug Delivery to Colon:
Several approaches are used for site-specific drug delivery for colon specific drug delivery system which include the following,

Primary approaches for colon targeted drug delivery system:
1. pH sensitive polymer coated drug delivery system.
2. Time controlled (delayed) release drug delivery system
3. Microbial triggered drug delivery
   i. Prodrug approach
   ii. Polysaccharide based system
4. New approaches for colon targeted drug delivery
   i. Pressure controlled drug delivery system (PCDDS)
   ii. CODE (combination of pH dependent and microbial triggered CDDS)
   iii. Osmotic controlled colon drug delivery system
   iv. Pulsatile colon targeted drug delivery: Pulsincap system and Port system
v. Azo hydrogel
vi. Multiparticulate system based drug delivery

**pH sensitive polymer coated drug delivery system:**

In the stomach, pH ranges between 1 and 2 during fasting but increases after eating. The pH is about 6.5 in the proximal small intestine and about 7.5 in the distal small intestine. From the ileum to the colon, pH declines significantly. It is about 6.4 in the cecum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers. The pH in the transverse colon is 6.6 and 7.0 in the descending colon. Use of pH dependent polymers is based on these differences in pH levels. The polymers described as pH dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises. Although a pH dependent polymer can protect a formulation in the stomach and proximal small intestine, it may start to dissolve in the lower small intestine and the site-specificity of formulations can be poor. The decline in pH from the end of the small intestine to the colon can also result in problems, lengthy lag times at the ileocecal junction or rapid transit through the ascending colon which can also result in poor site-specificity of enteric-coated single-unit formulations. Most commonly used pH dependent coating polymers are methacrylic acid copolymers, commonly known as Eudragit S, more specifically Eudragit L and S. Colon targeted drug delivery systems based on methacrylic resins has described for insulin, prednisolone, quinolones, salsalazine, cyclosporine, beclomethasone dipropionate and naproxen. Dissolution studies performed on the mesalazine tablets further confirmed that the release profiles of the drug could be manipulated by changing the Eudragit L100-55 and Eudragit S100 ratios within the pH range of 5.5 to 7.0 in which the individual polymers are soluble respectively, and a coating formulation consisting of a combination of the two copolymers can overcome the issue of high GI pH variability among individuals.

![Fig. No. 02: Release pattern of a multilayer coated system at different pH conditions in GIT](image)

*Fig. No. 02: Release pattern of a multilayer coated system at different pH conditions in GIT*

*Citation: Nalanda T. Rangari et al. Ijppr.Human, 2015; Vol. 3 (1): 167-186.*
**Time controlled (delayed) release drug delivery system:**

Time controlled release system such as sustained or delayed release dosage forms are also very promising. The transit time varies in different parts of gastrointestinal tract. This transit time is responsible for the delayed release of drug. The main drawbacks of this delivery system are that the transit time varies from one person to other and amount of food intake. However due to potentially large variation of gastric emptying time of dosage forms in humans, in this approach colon arrival time of dosage forms can not accurately predicted, resulting in poor colonical availability. The dosage forms may also applicable as colon targeting dosage forms by prolonging the lag time of about 5.5 hours (range 5 to 6 hours). Disadvantages of this system are-(i) Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.(ii) Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug. (iii) Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhea and the ulcerative colitis.

**Microbial triggered drug delivery:**

These systems are based on the exploitation of the specific enzymatic activity of the microflora (enterobacteria) present in the colon. The colonic bacteria are predominately anaerobic in nature and secrete enzymes that are capable of metabolizing substrates such as carbohydrates and proteins that escape the digestion in the upper GI tract. The enzymes present in the colon are: 1. Reducing enzymes: Nitroreductase, Azoreductase, N-oxide reductase, sulfoxide reductase, Hydrogenase etc., 2. Hydrolytic enzymes: Esterases, Amidases, Glycosidases, Glucuronidase, sulfatase etc. The vast microflora fulfils its energy needs by fermenting various types of substrates that have been left undigested in the small intestine, e.g. di- and tri-saccharides, polysaccharides etc. For this fermentation, the microflora produces a vast number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase. Because of the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon-specific drug delivery seems to be a more site-specific approach as compared to other approaches. These polymers shield the drug from the environments of stomach and small intestine, and are able to deliver the drug to the colon. On reaching the colon, they undergo assimilation by micro-organism, or degradation by
enzyme or break down of the polymer back bone leading to a subsequent reduction in their molecular weight and thereby loss of mechanical strength. They are then unable to hold the drug entity any longer.

**Prodrug approach:**

Classical prodrugs design often represents a non-specific chemical approach to mask unwanted drug properties such as low bioavailability, less site specific, and chemical instability. On the other hand, targeted prodrug design represents a new strategy for directed and efficient drug delivery. Particularly, prodrugs targeting to a specific enzyme or a specific membrane transporter, or both, have potential drug delivery system especially for cancer chemotherapy. Prodrug is the main approach of microbial triggered drug delivery system in which the drug release from the formulation is triggered by the microflora present in the gut. Prodrug is the inactive form of an active parent drug that undergoes enzymatic transformation to release the active drug. The produrgs are prepared by linking the active drug with hydrophobic moieties like amino acids, glucoronic acids, glucose, galactose, cellulose, etc.

These prodrug molecules get hydrolysed in the presence of the enzymes released by the microflora or a specific membrane transporter, or both, have potential drug delivery system especially for cancer chemotherapy.

![Fig. No. 03. Prodrug approach](image)

**Targeting specific enzymes:**

Glycoside derivatives are hydrophilic and are poorly absorbed from small intestine, but once they reach colon, they can be effectively liberated by bacterial glycosidases to release the free drug and facilitates the absorption by the colonic mucosa. Glycosidic prodrug, dexamethasone
glucoside appeared to be better candidate, about 60% of the prodrug reach caecum as a free steroids, while parent drug were absorbed in small intestine.

**Targeting specific membrane transporters:**

When free steroids were administered orally, they were almost absorbed in the small intestine and less than 1% of the oral dose reached the colon. Nakamura et al. studied the conjugation of drug molecule to the polar amino acids and prepared prodrugs for colon drug delivery. Proteins and their basic units, i.e. the amino acids, have polar groups like -NH2 and - COOH. These polar groups are hydrophilic and reduce the membrane permeability of amino acids and proteins. Various non-essential amino acids such as glycine, tyrosine, methionine, and glutamic acid were conjugated to salicylic acid. The conjugate showed minimal absorption and degradation in the upper GI tract and showed more enzymatic specificity for hydrolysis by colonic enzymes. Glucuronide and sulphate conjugation is the major mechanism for the inactivation and preparation for clearance of many drugs. Bacteria of the lower GI tract, however, secrete β-glucuronidase and can deglucuronidate a variety of drugs in the intestine. The azo linkage exhibits a wide range of thermal, chemical, photochemical and pharmaceutical properties. The azo compounds are extensively metabolised by the intestinal bacteria, both by intracellular enzymatic components 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 prodrugs. Sulphasalazine, which was used for the treatment of rheumatoid arthritis, was later known to have potential in the treatment of inflammatory bowel disease (IBD). This compound has an azo bound between 5- ASA and sulphapyridine.

**Polysaccharide based system:**

The polysaccharide which is polymer of monosaccharide retains their integrity, because they are resistant to digestive action of GI enzymes, matrices of polysaccharide are assessed to remain intact in physiological environment of stomach and small intestine, as they reach colon they are acted upon bacterial polysaccharidases and results in degradation of the matrices. Family of natural polysaccharide has appeal to area of drug delivery as it comprised of polymer with large number of derivitizable groups, with wide range of molecular weight, varying chemical composition and forms most low toxicity and biodegradability, yet a high stability. Pectin is a polysaccharide which contain α- 1, 4 Dgalactouronic acid and 1, 2 D-Rhamnose with D-
galactose & D-arabinose side chains. A novel colonic drug delivery is investigated. In vitro experiments demonstrated that high methoxy pectin, when applied as compression coat, proved capable of coat tablet during condition stimulating gastrointestinal environment and was susceptible to enzymatic attack. In vivo gamma scintigraphic studies confirmed the in vitro findings the pectin coating tablets indicate that disintegrating in the colonic region, and illustrated that degradation by microflora, thus necessities in the development of such derivatives of pectin which is less water soluble, Calcium pectinate, the insoluble salt of pectin was used for colon targeted drug delivery of Indomethacin. The use of pectinolytic enzymes to stimulate breakdown in colon showed that pectin/chitosan mixture was susceptible to enzymatic breakdown and releasing its content. Some studies carried out to access the potential pectin:chitosan films for colonic delivery found that pectin alone was able to protect the premature release, but only when a substantially thick coat was provided. Some researcher reported that pectin HPMC compressed core tablets of 5- ASA for colon delivery. Drug dissolution/ system erosion/ Degradation studies were carried out in pH 1.2 and 6.4 buffers using pectinolytic enzymes, system was designed that transit time from the GI tract and arrival time for colon is 6 h. It was found that pectin alone was not sufficient to protect the core tablets and HPMC addition was required to control the stability of pectin. The optimum concentration of 20% HPMC was preferred for 6 h that corresponds to 25-30% erosion and after the influence of the pectinase systems degrades faster and release 5-ASA to the colon.

New approaches for colon targeted drug delivery:

Pressure controlled drug delivery system (PCDDS):

Digestion mainly occurs due to the contractility of the stomach and peristaltic movement of the intestine. The contractility movement of stomach leads to the digestion or breakdown of larger particles to smaller ones which are then transferred to intestine. The peristaltic movement of intestine is responsible for the passage of bolus from one part of GIT to the next part. The peristaltic movement of ascending colon transfers the bolus to transverse colon called as mass peristalsis. These peristaltic movements occur in limited number i.e. three to four times a day. These peristaltic movements of intestine results in an increase in the luminal pressure. This increase in luminal pressure is the key point in the development of pressure controlled drug delivery system. The pressure controlled drug delivery system 25 consists of a capsule in which
the drug is present. These gelatine capsules are coated with water insoluble polymer like ethyl cellulose on their inner side. The drug is introduced into the capsule along with suppository base. The thickness of ethyl cellulose coating determines the disintegration capacity of the capsule. After administration the suppository base dissolves at body temperature. The water from intestinal contents is absorbed resulting in increased viscosity which leads to an increase in the pressure in the capsule. The pressure in the capsule expels the drug into the colon. The intestinal pressure developed varies with the circadian rhythms, state of body, food administration, etc.

**CODE (combination of pH dependent and microbial triggered CDDS)**

This method is developed to minimize the problems associated with the pH and time dependent drug delivery systems. In this system the pH sensitive polymers are used along with the polysaccharides that are degraded only by specific bacteria present in the intestine. This system consists of a core tablet coated with three layers of polymer coatings. The outer coating is composed of the polymer Eudragit L. This coating gets dissolved once the tablet passes though the pyloric and duodenum and exposes the next coating. The next coating is composed of Eudragit E. This layer allows the release of lactulose present in the inner core. This released lactulose gets metabolized into short chain fatty acids that lower the surrounding pH where the Eudragit E layer dissolves. The dissolving of Eudragit E results in the exposure of the drug. The other polysaccharides that are used along with the drug in the core tablet are mannitol, maltose, etc. The bacteria present in the colon are responsible for the degradation of polysaccharides that are released from the core tablet. The degradation of polysaccharides results in organic acids formation that lowers the pH of the contents surrounding the tablet.

![CODE System Diagram](image)

**Fig. No. 04. CODE System**

_Citation: Nalanda T. Rangari et al. Ijppr.Human, 2015; Vol. 3 (1): 167-186._
Osmotic controlled colon drug delivery system:

This system consists of osmotic units. The osmotic units are used either singly or as many as 5-6 push pull units that are encapsulated in a hard gelatin capsule. The push pull units are bilayered with outer enteric impermeable membrane and inner semi permeable membrane. The internal or central part of the push pull consists of the drug layer and push payer. The semipermeable membrane which is present next to the drug layer consists of an orifice through which the drug contents are expelled during the course of time. The capsule body enclosing the push pull units gets dissolved immediately after administration. During the passage of the push pull units through the GIT the enteric impermeable membrane prevents the water absorption into the unit. The coating gets dissolved once it reaches the small intestine due to higher pH (>7). Water enters the unit through the semi permeable membrane causing the push layer to swell. The swelling of the push compartment forces the drug into the surrounding environment through the orifice. These osmotic controlled drug delivery systems deliver the drug at a constant rate for up to 24hr.

![Fig. No. 05: Osmotic controlled colon drug delivery system](image_url)

Pulsatile colon targeted drug delivery: Pulsincap system and Port system

Pulsincap system:

In this system the formulation is developed in a capsule form. The plug placed in the capsule controls the release of the drug. Swellable hydrogels are used to seal the drug contents. The capsule gets swelled when it comes in contact with the dissolution fluid and after a lag time the plug gets pushed off from the capsule and the drug will be released. Polymers such as different
grades of hydroxyl propyl methyl cellulose (HPMC), poly methyl methacrylate and polyvinyl acetate are used as hydrogel plugs. The lag time is controlled by the length and point of intersection of the plug in the capsule body.

![Figure 06: Drug release mechanism of Pulsincap system](image)

**Fig. No. 06: Drug release mechanism of Pulsincap system**

**Port system:**

In this system the capsule body is enclosed in a semipermeable membrane. The capsule body consists of an insoluble plug consisting of osmotically active agent and drug formulation. When the capsule comes in contact with the dissolution fluid the semipermeable membrane permits the fluid flow into the capsule resulting in the development of pressure in the capsule body which leads to release of drug due to expelling of the plug. The drug is released at regular intervals with time gap between the successive intervals.

![Figure 07: Drug release mechanism of Port system](image)

**Fig. No. 07: Drug release mechanism of Port system**

Azo hydrogel:
The pH sensitive monomers and azo cross linking agents in the hydrogel produce the colon specificity. During their passage through the GIT these hydrogels swell as the pH increases. This swelling of hydrogels cleaves the cross links in the hydrogel network causing the release of drug entrapped in the hydrogel. These hydrogels are prepared by cross linking polymerization of N-substituted (meth) acrylamides, N- tert- butyl acrylamide and acrylic acid with 4, 4-di (methacryloylamino) azobenzene as cross linking agents. The hydrogels are also prepared by cross linking polymeric precursors, polymer-polymer reaction using same polymeric precursor with the corresponding copolymer containing side chains terminating in NH₂ groups. The degradation rate of hydrogel is associated with the degree of swelling and inversely proportional to the cross linking density.

Multiparticulate system based drug delivery:
The various advantages of multiparticulate systems are increased bioavailability, reduced risk of local irritation, reduced risk of systemic toxicity. The various multiparticulate approaches include pellets, microparticles, granules and nanoparticles. Multiparticulates systems are preferred over single unit dosage forms as the multiparticulate systems enable the drug to reach the colon quickly and retained in colon for long period of time. These systems pass through the GIT easily due to their smaller size. Multiparticulate systems are dispersed more uniformly in the GIT resulting in more uniform drug absorption. Nanoparticles, the preparation of nanoparticles is simple and these are capable of protecting the protein and peptide drugs from the chemical and enzymatic degradation in GIT resulting in an increase in their stability and absorption of through the intestinal epithelium. The polymeric nanoparticles are prepared by various techniques like polymerization, nanoprecipitation, inverse microemulsion. The methods involve the use of organic solvents, heat and agitation. The drawback of these methods is that the heat, agitation is harmful to proteins and peptide drugs. Ionic gelation technique is the most widely used method for proteins and peptide drugs.

Evaluation test of Colon Drug Delivery System

In vitro evaluation

No standardized evaluation technique is available for evaluation of CDDS as an ideal in vitro
model should possess in vivo conditions of GIT such as pH, volume, stirring, bacteria, enzymes, enzyme activity and components of food. These conditions are influenced by diet and physical stress. The in vitro evaluation of colon targeted drug delivery systems includes the in vitro dissolution study and in vitro enzymatic test.

**In vitro dissolution test**

The dissolution testing is done using the conventional basket method. The dissolution testing is done in different buffers to characterize the behaviour of formulations at different pH levels. The different media that are used for the dissolution testing of colon targeted drug delivery are pH 1.2 to simulate gastric fluid, pH 6.8 to simulate small intestine, pH 7.4 to simulate large intestine. The colon targeted drug delivery systems are tested for 2hr in 0.1N HCl, 3hr in pH 6.8 phosphate buffer and finally at pH 7.4 phosphate buffer. Buffers of the above pH are prepared to evaluate the colon targeted drug delivery systems.

**In vitro enzymatic test**

There are 2 tests for the in vitro enzymatic test.

- The carrier drug system is incubated in fermenter containing suitable medium for bacteria. The amount of drug released at different time intervals is determined.
- Drug release study is performed in buffer medium containing enzymes pectinase, dextranase or rat or guinea pig or rabbit cecal contents. The amount of drug released in a particular time is directly proportional to rate of degradation of polymer carrier.

**In vivo evaluation**

The in vivo evaluation of the CDDS is done in dogs, guinea pigs, rats and pigs as they resemble the anatomic and physiological conditions, micro flora of human GIT. The distribution of various enzymes in GIT of rat and rabbit is comparable to that in human.

**CONCLUSION**

The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. Colon targeted drug delivery system offers benefits of local and systemic effects. The main advantage of CDDS is that the colon offers near neutral pH, a long transit time, reduced
enzymatic activity and increased responsiveness to absorption enhancers. Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. Considering the sophistication of colon-specific drug delivery systems, and the uncertainty of current dissolution methods in establishing possible in vitro/in vivo correlation, challenges remain for pharmaceutical scientists to develop and validate a dissolution method that incorporates the physiological features of the colon, and yet can be used routinely in an industry setting for the evaluation of CDDS.

REFERENCES

