# A review on novel approaches for colon targeted drug delivery systems

Sumedha Saxena, Chandan Kumar Singh*, Mukesh Yadav, Alex Laurel Samson
Department of Pharmacy,
Dr. M.C. Saxena College of pharmacy,
Lucknow, U.P, India
*chandansingh.skic@gmail.com*

**ABSTRACT**

This review mainly focus on targeted drug delivery to the colon is extremely desirable for local treatment of inflammatory bowel disease such as ulcerative colitis, crohn's disease, amoebiasis, colonic cancer as well as for systemic delivery of protein and peptide drugs. The colon is a site where local delivery allows topical treatment of inflammatory bowel disease and systemic delivery of drug can take place. Treatment of colon can be made effective if the drug can be targeted directly into the colon because drug release and absorption should not be take in abdomen and the small intestine and bioactive agents should not be degraded and to allow drug release into the colon. Drug targeting to the colonic area is not only associated with the treatment of colonic ailment locally but also delivering drugs such as protein and peptide for their systemic effects which are degraded and bioavailability is very depressed due to the instability in the GI Tract.

**Keywords:** Colon targeted drug delivery system, Crohn's disease, pH and time dependent system, Drug Carrier, Pro-drug.

## INTRODUCTION

Colon targeted drug delivery system may be following the concept of control or sustained route for drug administration has received more attention (Vinay *et al.,* 2012). At least 50% of the dosage forms available in the market are oral dosage form because these system have more advantage due to high patient compliances (Akhil *et al.,* 2011) Targeted dreg delivery into the colon is highly desirable for local treatment of a variety of bowel disease. Like crohn's disease, colonic cancer ulcerative Colitis, amebiosis and many others disorders ((Anil and Betty, 2010). Colon targeted drug delivery system is not only the suitable for delivering the drug to the colon for local treatment but it is also a preferable approach for delivery of protein and peptide and enhance their bioavailability (Amidon *et al*., 2015). Bioavailability of protein and peptide may be achieved if it can be protected from acid and enzymes in the stomach and upper intestine and released and absorbed in the colon and protect it form degradation in stomach (Prasanth *et al*., 2012). Degradation of such drug in stomach can be prevent by using some polymer either alone or in a combination because polymer effect the rate of release and absorption of drugs and play an important role in formulation of colon targets drug delivery system (H. Rajpurohit *et al*., 2010). Oral route is the more preferable and convenient route but other routes for colon drug delivery system may be used. Administration of drug through the rectum offers the shortest route for targeting drugs to the colon still reaching the colon proximal part via rectal administration is difficult. Rectal administration is difficult and painful for patient thus patient compliances decreased (Massimo Campieri *et al*., 1992). Colon contain a variety of bacteria which is responsible for azo reduction and enzymatic cleavage which is responsible for the metabolism of many drugs (Sai Mansa *et al*., 2015)

## CHOICE OF POLYMER FOR CTDDS

Delivery of drugs to the colon lead on much interest for local and systemic treatment of variety of colonic disease because of various therapeutic advantage of colon like near neutral and longer transit time. Advantageous delivery of a drug to the colon depend upon protection of the drug from degradation or release in the stomach which can be achieved by using polymer because polymer can influence the

**How to cite this article:** Saxena S, Singh C, Yadav M, Samson AL; A review on novel approaches for colon targeted drug delivery systems; PharmaTutor; 2018; 6(7); 11-22; http://dx.doi.org/10.29161/PT.v6.i7.2018.11

rate of release and absorption of drug and have an important role in formulating CTDDS. Both natural and biodegradable polymers are preferred for drug delivery application. The advantage for natural and biodegradable polymers are-

- In expensive and available in variety of structure.
- Biodegradable polymers are broken down into biologically acceptable molecules that are metabolized and removed from the body via normal metabolic pathway.

So that the choice of polymer for formulating colon targeted drug delivery system is playing a vital role. (H. Rajpurohit *et al*., 2010); ( Neha Sharma and harikumar,2013)

## ADVANTAGE OF CTDDS OVER CONVENTIONAL DRUG

- Colon have less peptidase activity so peptides, insulin oral vaccines, growth hormones can be delivered through this route (Shruti, 2007).
- Colon is ideal site for the delivery of agents to treat the local disease of the colon (Mahesh,2014)
- Required small drug quantities due to locality targeting (Akhil, 2011).
- Reduces dosage frequency Hence lower cost of expensive drugs.
- Possible leading to a reduced incidence of side effects and drug interactions.
- The colon is an attractive site where poorly absorbed drug molecules may have an improved bioavailability.
- Reduce gastric irritation caused by many drugs like NSAIDS.
- Bypass initial first pass metabolism.
- Extended daytime of night time activity.
- Improve patient compliance.
- It has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drug (Mahesh *et al*.,2014); (N.K. Jain, 2001); (M. Halsa,2001); (Rennat,1998; )

## LIMITATION OF COLON TARGETING DRUG DELIVERY SYSTEM-

- Multiple manufacturing steps.
- Incomplete release rate.
- Bioavailability of drug may be low due to potentially binding of a drug in a nonspecific way to dietary residue, fecal matter, mucus and intestinal secretion.
- The resident micro flora could also affect colonic performance via metabolic degradation of the drug.
- Non availability of an appropriate dissolution testing method to evaluate the dosage form in-vitro (Akhil *et al.,* 2011); ( Sukhbir *et al.,*2013).
- Drug should be in the solution form before absorption and there for rate limiting step for poor soluble drugs.
- An important limitation of the PH sensitive coating technique is the uncertainty of the location and environment in which the coating may start to dissolve. Normal in the patient with ulceration colitis (M.K. Ratnaparkhi *et al.,* 2013).
- Limitation of pro-drug approach is that it is not very versatile approach as it's formulation depends upon the functional group available on the drug moiety for chemical linkage.(Gaurav *et al*., 2010).

TABLE No. 01-Colonic diseases, its sites and active drug components. (Danda and chandan, 2013)

| Targeted site | Disease | Drug |
|---|---|---|
| Topical | Inflammatory bowel diseases (Crohn's disease, ulcerative colitis), Irritable bowel diseases, Amoebiasis | Hydrocortisone, Prednisolone, Sulfasalazine, Mesalazine, Mercaptopurine, Metronidazole, Mebendazole, Tinidazole |
| Systemic | Oral delivery of peptide, oral delivery of vaccines, to prevent gastric irritation, To prevent first pass | Typhoid, NSAIDS, Steroids, Insulin |

| | | |
|---|---|---|
| | metabolism of orally administered drug | |
| Local | Pancreatactomy, Colorectal cancer, cystic fibrosis, Chronic pancreatitis | 5- Fluorouracil, digestive enzymes |

**ANATOMY OF COLON (Prabhakar *et al*., 2012) (Anne and Allison, 2010)**

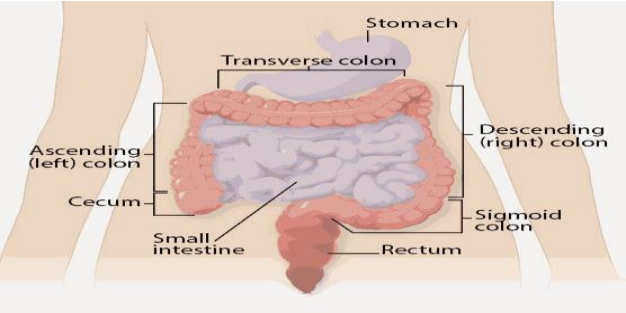



Figure 01- Colon

The digestive system is the collective name used to describe the alimentary canal, its accessory organs and a variety of digestive process. The alimentary canal begin at the mouth, passes through the thorax, abdomen and pelvis and ends at the anus.

The large intestine is about 1.5 meters long, beginning at the caecum in the right iliac fossa and terminating at rectum and anal canal deep in the pelvis. Human large intestine is about 1.5 meter long. the colon is a cylindrical tube which is linked by moist, soft pink lining called mucosa. The colon has four parts which are same structure and function.

**Ascending Colon-**It is nearly 12.5cm, in length. It extends from the caecum to the hepatic flexure.

**Transverse Colon-** The ascending colon further continues as the transverse colon, form the hepatic flexure to the splenic future.

**Descending Colon-** The transverse Colon descends down to form the descending colon. It begins at the splenic mixture and terminates at the beginning of the sigmoid colon.

**Sigmoid Colon-** The descending colon continue as an S-Shaped Sigmoid colon, terminating at the rectum.

Table No. 02- Length of Various Parts of Large Intestine.

| 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 |

**EFFECT OF COLONIC BACTERIAL FLORA (Sujit K. Chaudhari, 2014)**

**Beneficial Effects**

- Colonic bacterial flora produce many vitamins include vitamin K and some member of vitamin B complex including folic acid.
- Colonic bacteria produce short chain fatty acids (SCFA's) which prevent colorectal cancer.

**Harmful effects:-**

- The bacterial overgrowth in the ileum can developed diarrhea, Mal absorption syndrome and anemia.
- The Colonic bacterial flora (some species) can produce ammonia which is not absorbed in hepatic failure and precipitate hepatic encephalopathy

## FACTOR AFFECTING COLON TARGETED DRUG DELIVERY SYSTEM

The factors that affect the Colon targeting are categorized in two categories:-

- Physiological factors
- Pharmaceutical factors

**1. PHYSIOLOGICAL FACTORS:-**

The factor which involve physiologically in drug delivery and responsible for affecting the targeting of drug to the colon are:-

**Gastric emptying (Danda and chandan, 2013)**

Drug delivery to the colon upon oral administration depend mainly on gastric emptying and bowel transit time i.e. upon reaching the colon the transit time of drug depends on the nature and size of the particles.

Larger particles have less transit time as compared to smaller particles.

| Sr. No | Part of GIT | Transit Time |
|---|---|---|
| 1 | Fasted State | 10min- 2hr |
| 2 | Fed State | 2 hr |
| 3 | Small intestine | 3-4 hr |
| 4 | Colon transit | 20-35 hr |

**pH of colon**

The pH of the Gastrointestinal tract is subjected to both inter and intra subject variation. Disease state, Diet and food intake influence the pH of GI Tract. This changes in the pH in different parts of GIT is the basic for the development of Colon targeted drug delivery systems. Coating with different polymers is done to target the drug to the site. (M. Prathap *et al*., 2014)

**Table No. 03- PH in different parts of Colon**

| Part of GIT | pH |
|---|---|
| Stomach | Fasted state<br>1.5 - 2<br>Fed state<br>2.6 |
| Small Intestine | 6.6 – 7.5 |
| Colon<br>Ascending Colon<br>Transverse Colon<br>Descending Colon | <br>6.4<br>6.6<br>7.0 |

**C) Colonic micro Flora and enzymes (Cynthia and Wendy, 2015); (Danda andChandan, 2013); (M. Prathap *et al*., 2014)**

The Gastrointestinal Contain a variety of microorganism that produces many enzymes need for metabolism. Growth of this micro flora is controlled by the GIT Contentment's and peristaltic movements. The enzyme released by different microorganism E. Coli, Clostridia, Lactobacilli, Eubacteria, Streptococci are responsible for the various metabolic reaction that take place in GIT.

**Table No. 04- Different micro flora, enzymes released and action**

| Microorganism | Enzyme | Metabolic Reaction |
|---|---|---|
| E.Coli, Bacteroids | Nitroreductase | Reduce aromatic and heterocyclic nitro compounds |
| Clostridea, Lactobacilli | Hydrogenase | Reduce carbonyl group and aliphatic double bond. |
| Clostridia, Eubacteria | Glycosidase | Clevage of B-glycosides of alcohols and phenol |
| Eubacteria Clostridia Streptococci | Sulfates | Cleavage of O-Sulphate and Sulfamates |

**2. PHARMACEUTICAL FACTORS-**

The Various Pharmaceutical factors are-

**Drug Candidates:** Drugs which show poor absorption from the stomach or intestine including peptide are most suitable for CDDS. The drug used in the treatment of IBD, ulcerative Colitis, diarrhea and colon cancer are ideal character for local colon delivery. (Mahesh *et al*., 2014). Due to high retention time of colon, colon causes an increase in the absorption an increase in the absorption of poorly absorbed agents (M. Prathap *et al.,* 2014)

**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 drug and the type of absorption enhancers choosen influence the carrier selection, Moreover the choice of drug carrier depends on the functional groups of drug molecule. (Mukesh *et al.,* 2013)

## DIFFERENT APPROACHES USED FOR COLON TARGETING-

**1. Primary approaches of colon specific drug delivery-**

a) PH Sensitive polymer coated drug delivery system.
b) Delayed (Time Controlled release System) release drug delivery system.
c) Microbial triggered system
d) Pro-drug approach for drug delivery to colon
e) Polysaccharide based delivery system.

**2. Newly developed approaches for CDDS-**

a) Pressure Controlled drug – delivery system.
b) Pulsatile colon targeted drug delivery.
   i) Pulsin Cap system
   ii) Port System.
c) CODES technology
d) Osmotic controlled drug delivery (OROS-CT)
e) Multiparticulate system based drug delivery.
f) Azo hydrogels.
g) Probiotic approach.

**1. PRIMARY APPROACHES OF COLON SPECIFIC DRUG DELIVERY-**

**A. pH Sensitive polymer coated drug delivery system.**

There is numerous invention approaches have been discovered to develop colon- difference in the pH along the GI tract is one of the approaches to achieve colon targeting. So the polymer has specific solubility at equivalent pH is beneficial for colon targeting however, a pH dependant polymer can shield a formulation in the stomach, and proximal small intestine, it start to dissolve in the colon (Ashish, 2018). A multiple range of mechanisms have been developed to attain colon targeting of drugs. Mostly used mechanisms are to coat the formulation using natural or synthetic polymer (M. Prathap *et al*., 2014). In this mechanism, the drug is intended in the core of the formulation which is coated with PH sensitive Polymer. The first coating is an acid soluble polymer and outer coating is an enteric polymer (Chaurasia and Jain, 2008). The core of formulation is comprised of the API and excipients. When the drug pass through the GI tract the formulation does not degraded or release in the stomach due to enteric coating, but the enteric coating will dissolve in the small intestine, where the PH is above 6. When the drug reaches to the colon, the bacteria enzymetically degrade the polysaccharide into organic acid. This lowers the PH of the surrounding system and causes the dissolution of the surrounding system and results in dissolution of the surrounding system acid soluble coating and subsequent drug release (Neha and S.L., 2013). The most commonly used pH dependent polymers are derivatives of acrylic acid and cellulose (Nishant and Dr. R.C., 2012).

Table No. 05- Showing different PH sensitive polymers and their threshold pH release (Gurmeet *et al.,* 2012)

| S.No. | Polymer | Threshold PH |
|---|---|---|
| 1 | Eudragit S-100 | 7 |
| 2 | Eudragit PL-100 | 6 |
| 3 | Eudragit Fs30D | >7 |
| 4 | Hydroxypropylmethy Cellulose phthalate | >5.5 |
| 5 | Shellac | 7 |
| 6 | Eudragit L100-55 | 5.5 |

**B. Delayed (Time controlled release system) release drug delivery system.**

Time dependent / Controlled release system such as sustained or delayed release dosage form are also very promising drug release system However due to potentially large variations gastric emptying time of dosage forms in humans, in these approaches, Colon arrival time of dosage forms cannot be accurately predicted, resulting in poor colonial availability (Threveen *et al*., 2011). The strategy in designing time released systems is to resist the acidic environment of the stomach and to undergo a lag time of predetermined span of time, after which release of drug take place the lag time in this case is the time required to transit from the mouth to colon a lag time of 5 hours is usually considered sufficient since small intestine is about 3-4 hours, which is relatively constant and hardly affected by the nature of formulation administered. (Mukesh *et al.,* 2013)

**Disadvantages of this system are-**

- Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.
- GIT movement would result in the change in gastrointestinal transit of the drug.
- Accelerated transit through different region of the patient with the carcinoid syndrome, diarrhea and ulcerative Colitis. (M. Prathap *et al*., 2014)

**C. Microbially triggered system**

Targeting of drugs to the colon is effective and safe for the treatment of various colonic disease. These diseases are often poorly and inefficiently managed either by oral route in which oral drugs are largely absorbed before they rich the colon or by the rectal

route of administration which is less acceptable. Microbial triggered delivery system is most convenient and highly site specific approach for targeting drug to the colon than all targeting system. Drug release when the polysaccharides are degraded by the bacteria of the colonic micro flora (Rupali *et al*., 2015). The upper part of GIT i.e the stomach and the duodenum has a micro flora of less than $10^3 - 10^4$ CFU /ml. the micro flora of Colon on the other side is is the range of $10^{11}$-$10^{12}$ CFU/ml consisting mainly of anaerobic bacteria. E.g. Bactericides, Bifid bacteria, Eubacteria, Clostridia Enterococci, Enterobacteria ect. Vast number of enzymes like glucuronidase, xylosidase, arabimosidas, arabimosidase, galactosidase, nitroteductase, azoreductase, deaminase and urea dehydroxylase are produce by micro flora Because of the presence of these biodegradable enzymes, only in the colon, the use of bacterial degradable polymers for colon specific drug delivery seems to be a more site specific approach as compared to other approaches (M. Mallikarjuna *et al.,* 2012).

**D. Pro-drug approach for drug delivery to colon**

Pro-drug are pharmacologically inactive chemical derivatives that could be used to alter the physiochemical properties of drug in a temporary manner or to increase their usefulness and to decrease associated toxicity. A pro-drug is a compound formed by chemical modification of biologically active compound that will liberate the active compound in vivo by enzymatic or chemical processes (Vimal and Vikram, 2012). Pro-drug is the main approach of microbial triggered drug delivery system is system in which the drug release from the formulation is triggered by the micro flora present in the gut. (M. Prathap *et al*., 2014). Biotransformation is carried out by a variety of enzymes, mainly of bacterial origin, present in the colon. The enzymes that are mainly targeted for colon drug delivery include azoreductase-galactosidase, B-xylsidase, nitroreductases. Generally, a pro-drug is successful as a colon drug carrier of it is hydrophilic and bulky, to minimize absorption from the upper GI tract and once in the colon, it is converted into a more lipophilic drug molecule that is then available for absorption (Threveen *et al.,* 2011). A clinical study ha shown clear evidence that B-cyclodextrins are poorly digested in the small intestine but are almost completely degraded by the colonic microflora (C. Tuleu *et al.*, 2001).

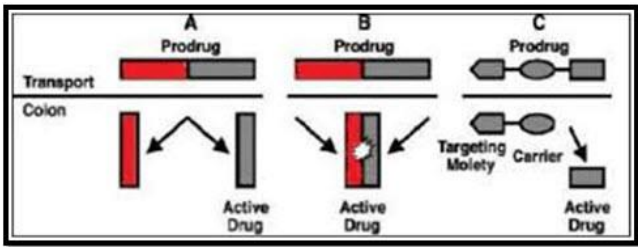



**Diagram 02- Pro-drug approach**

Table No. 06- Produrg evaluated for colon specific drug delivery (Threven *et al.,* 2011)

| Drug investigated | Carrier | Linkage hydrolgsed |
|---|---|---|
| 5-ASA | Azo conjugates, Sulphapyridine (SP) | Azo-linkage |
| Naproxane | Dextran conjugate | Ester linkage |
| Dexamethasone | Dextran conjugate | Using spacer |
| 5-ASA | Azo – Conjugates, Glycine | Amide linkage |

**E. Polysaccharide Based delivery system**

Polysaccharide based delivery system is the other form microbial triggered drug delivery system (M. Prathap *et al.,* 2014). the inability of GIT enzymes to digest certain plant polysaccharides is taken as an advantage to develop colon specific drug delivery system. The drug is embedded in the matrix core of the biodegradable polymer by compressing the blend of active drugs, a degradable the blend of active drugs a degradable polymer and additives (Ravi *et al*., 2009). Many natural polysaccharides such as chondroitin sulphate, pectin, dextran and more particularly guar gum etc. has started with basis of investigation for their potential in innovating colon specific drug delivery. These are led to break down by the colonic micro flora to simple saccharides (Vikash *et al*., 2015). They can be easily modified chemically, biochemically and are highly stable, safe, non-toxic, and hydrophilic and in addition are biodegradable. The use of naturally occurring polysaccharides is attracting a lot of attention for drug targeting the colon since these polymers are found in abundance, have wide

availability, inexpensive and are available in a variety of structures with varied properties (Amresh *et al*., 2016).

## 2. NEWLY DEVELOPED APPROACHES FOR CDDS

### A. Pressure Controlled drug-delivery system

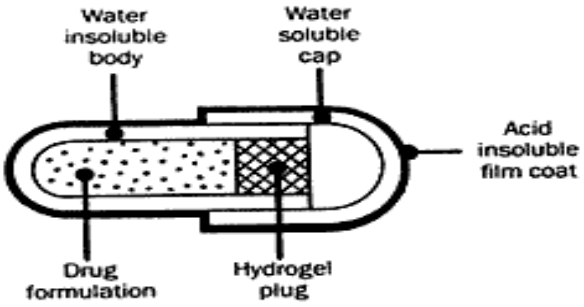
As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine Takaya *et al.* developed pressure controlled colon-delivery capsules prepared using ethyl cellulose, which is insoluble in water (Anil and Betty, 2010). Peristaltic motion causes the luminal pressure of the large intestine to increase more than that of the small intestine because its contents are more viscous due to the reabsorption of water. Several studies have been carried out to utilize the colonic luminal pressure to pressure to develop colon- specific drug delivery systems (S. Amidon *et al.,* 2015). the pressure controlled drug delivery system consists of a capsule in which the drug is present. These gelatin capsules are coated with water insoluble polymer like ethylcelluose on their inner side the drug is introduced into the capsule along with suppository base dissolves at body temperature the water from intestinal contents in absorbed resulting in increased viscosity which leads to an increase in the pressure in the capsule expels the drug into the colon (T. Nalanda and Prashant, 2015).

### B. Pulsatile colon targeted drug delivery

- Pulsin Cap system
- Port system

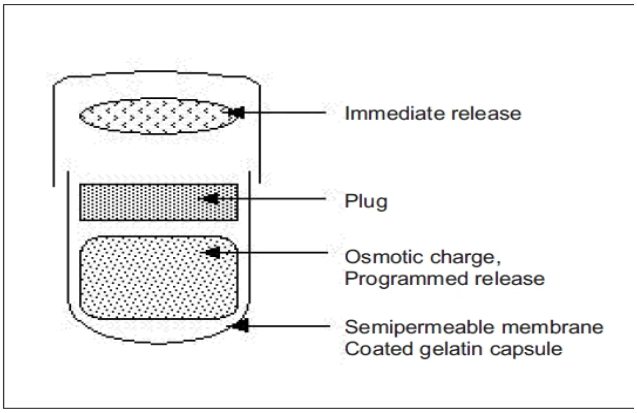
#### i) Pulsincap System

Pulsincap was developed by R.R. Scherer. International Corporation (Michigan) (Vikash *et al.,* 2011). 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 (Amit *et al.,* 2015). Polymers such as different grades of hydroxyl propyl methyl cellulose (HPMC), poly methyl methacrylate and polyvinyl acetate are used as hydrogel plugs. The log time is controlled by the lenth and point of intersection of the plug in the capsule body (Rama *et al.,* 2014).




Diag. 03- PulsinCap system

#### ii) Port System:



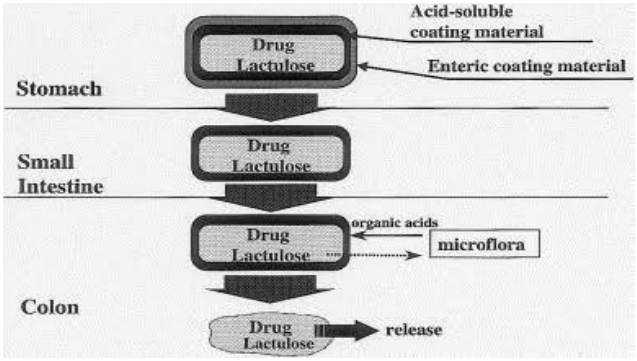

Diag. 04- Plan of Port System

The port system was developed therapeutic system research laboratory Ann Arbor, Michigan, USA, and consist of a capsule coated with a semi-permeable membrane, inside the capsule was an insoluble plug consisting of osmotically active agent and the drug formulation (Vipul and Moinuddin, 2012). When this capsule came in contact with the dissolution fluid, the semi-permeable membrane allowed the entry of water, which caused the pressure to develop and the insoluble plug expelled after a lag time. This system avoids second time dosing, which was beneficial for school children during daytime (J. Ali *et al*., 2006). The lag time is controlled by coating thickness. The system showed good correction in lag time of in-vitro and in-vivo experiments in humans (V.N.L. Sirisha *et al*., 2012).

### C. CODES technology (combination of PH dependent and microbially triggered CDDS)

CODES was designed to overcome the problems associated systems. In this system both the pH and microbially triggered approach are utilize the controls the drug release at desired location (Vipin *et al.,* 2012). It has been developed by utilizing a unique

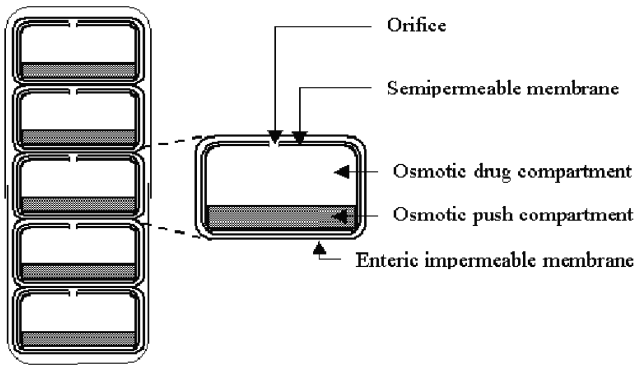
mechanism involving lactulose, which acts as a trigger for site specific drug release in the colon (Vinay *et al.,* 2012). It consists of core tablets coated with three layer of polymer coatings. The first coating is an acid soluble polymer (eudragit) and outer layer is enteric with a HPMC barrier layer in between to prevent any possible interaction between the oppositively charged polymers (Bhushan *et al.,* 2012). The premise of the technology is that the enteric coating protects the tablet while it is located on 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 affect the dissolution of the acid soluble coating and subsequent drug release (Anil and Betty, 2010). The other polysaccharide 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 (Brahma P. *et al.,* 2010).




Diag. 05- CODES System

**D. Osmotic Controlled Drug Delivery (OROS-CT)**

Osmotic controlled drug delivery (Alza corporation) is used as a once or twice a day formulation for targeted delivery of drugs to the colon. The OROS-CT can be a single osmotic agent or it can be comprised of as many as five to six push pull osmotic unit filled in a hard gelatin capsule(Brahma *et al*., 2010). After coming in contact with GI fluids, the gelatin capsule dissolves and the enteric coating prevents the entry of fluids from stomach into the system (Roop *et al*., 2014). The osmotic pumping action results when the coating dissolves in the high pH environment (pH>7) of the small intestine and the drug is delivered out of the orifice at a rate controlled by the rate of water transport across the membrane (K. Raja *et al*., 2015).




Diag. 06- OROS-CT

**E. Multiparticulate system based drug delivery**

Multiparticulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics (NS Dey *et al.,* 2008). The various advantages of this system are increased bioavailability, reduce risk of local irritation, reduce risk of systemic toxicity. The various multiparticulate approaches include pellets, micro particles, granules and nano-particles (Nalanda and Prashant, 2015). To administer or to recommend total dose these subunits are compressed into a tablets or filled into a sachets or encapsulated. These are capable of protecting the drugs from the chemical and enzymatic degradation in GIT resulting in an increase in their stability and absorption of through the intestinal epithelium (Bipin and Jagdish, 2013).

**F. Azo hydrogel**

The pH sensitive monomers and azo cross linking agents in the hydrogel produce the colon specificity. During their passage through GIT these hydrogels swell as the pH increase. This swelling of hydrogels cleaves the cross links in the hydrogel network causing the release of drug entrapped in the hydrogel (Rama Krishna *et al*., 2014). 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 degradation rate of hydrogen is associated with the degree of swelling and inversely

proportional to the cross linking density (Nalanda and Prashant, 2015).

**G. Pro-biotic approach:-**

The pro-biotic approach is one of the modern technique for colon targeting. In this approach three components are desirable namely probiotic strain, microbial digestible carrier and triggered temperature. Pro-biotic stains include inactive micro flora like bifidobacterium and lactobacillus species. At body temperature, these strains triggered to be active and start digesting the carrier and ultimately release the drug at desired place. This approach gains success in colon drug delivery system because these conditions are only available in colon (Prashant *et al*., 2010).

## EVALUATIONS

**In Vitro Evaluation-**

No standardized evaluation technique is available for evaluation of CDDS because an ideal in vitro model should possess the in vivo conditions of GIT such as PH, volume, stirring, bacteria enzymes, enzyme activity and other components of food. Generally these conditions are influenced by the diet and physical stress and these factors make it difficult to design a standard in vitro model. The in vitro evaluation of colon targeted drug delivery systems includes the in- vitro dissolution study and in vitro enzymatic test (Rama Krishna *et al.,* 2014).

**i) 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 behavior of formulation at different PH level (M. Prathap *et al*., 2014). The different media that are used for the dissolution testing of colon targeted drug delivery are PH 1.2 to stimulate gastric fluid, PH 6.8 to simulate small in testing, PH 7.4 to simulate large intestine. The colon targeted drug delivery are tested for 2 hour in 0.1N HCl, 3 hour 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 system. (Danda and Chandan, 2013)

ii) **In vitro enzymatic test-** These 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 release at different time intervals is determined.
- Drug released 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 time is directly proportional to rate of degradation of polymer Carrier (Archana and Divya, 2016).

**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. (K. Malleshwari and Vijaya, 2016)

## CONCLUSION

Colon targeted drug delivery system provide benefits of local and systemic effects. The main advantage of colon drug delivery system is that the colon offers a long transit time, near neutral PH, reduced enzymatic activity and increased responsiveness to absorption to absorption enhancers. The most critical challenge in CDDS is to preserve the formulation during its passage through the stomach and about six meters of small intestine. After seeking the limitation of different approaches, researchers invented various novel approaches. The novel approaches like pressure controlled drug delivery system, pulsincap system, port system, CODES, multiparticulate system, probiotic approach and azo hydrogels are more specific compared to primary approaches. Both natural and biodegradable polymers are used for the colon specific delivery of the drug. The need of today's business and patient community is to identify the appropriate approach that con result in the delivery of drugs in safe effective and less expensive manner with minimum fluctuation in term of release of drugs at target site.

**CONFLICT OF INTEREST:** Authors have no conflict of Interest.

## ↓ REFERENCES

1. Agarwal Vipin K., Gupta Amresh, Chaturvedi Shashank, Khan Farheen (2016); "Polysaccharide: carrier in colon targeted drug delivery system"; MIT International Journal of Pharmaceutical Sciences; 2(2); 1-9.
2. Ali J., Arora Shweta, Ahuja Alka, Baboota Sanjula, Qureshi J. (2006); "Pulsatile drug delivery system : An approach for controlled drug delivery; International Journal of Pharmaceutical Sciences; 68(3); 295-300.
3. Arora Vimal, Lohar vikram (2012); "Prodrug approach to better drug delivery"; International Journal of Pharmacentical Research; 4(1); 15-21.
4. Campieri Massimo, Corbelli Claudio, Gionchetti Paolo, Brignola Corrado (1992); "Spread and distribution of 5-ASA colnic foam and 5-ASA enema in patient with ulcerative colitis"; Digestive diseases and secienes; 37(12); 1890-1897.
5. Challa Threveen, Vynala Vinay, Allam Krishna Vamshi (2011); "Colon specific drug delivery system: A review on primary and novel approaches"; International Journal of Pharmaceutical Sciences Review & Research; 7(2); 171 - 181.
6. Chaudhuri Sujit K. (2014); "Concise Medical Physiology"; New Central Book Agency (p) Ltd., India; reprint edition; 126-127.
7. Chourasia M.K. Jain S.K (2004); "Polysaccharides for colon targeted drug delivery"; Drug Delivery and Therapeutics; 11(2); 129-148.
8. Dey NS, Majumdar S., Rao MED (2008); " Multiparticulate drug delivery System for controlled release"; Topical Journal of Pharmaceutical Research; 7(3); 1067-1075.
9. Dhir kushal, kahlon Harminder pal singh, kaur Sukhbir (2013); " Recent approaches for colon targeted drug delivery system"; International Journal of Pharmaceutical Chemical and Biological Sciences; 3(2); 360-371.
10. Dhyani Archana, Jugal Divya (2016); "Colon targeted drug delivery system: A review on primary and novel approaches"; International Journal of Pharmaceutical Science and Research; 1(5); 90-97.
11. Ghandhi Bipin, Baheti Jagdish (2013); "Multiparticulates drug delivery systems: A Review"; International Joural of Pharmaceutical and Chemical Sciences; 6(10); 1620-1626.
12. Ghosh Prashant Kumar, Gupta Vipin B., Gondoliya Bhavik, Rathore Mahendra Singh (2010); "Probiotic-assisted colon-specific delivery of diclofenac sodium from guarfum matrix tablets : In vitro evaluation"; Asian Journal of Pharmaceutics; 173-178.
13. Gouda M. Mallikarjuna, Shafaraya A. Ramakrishna, kumar SM Shanta (2012); "Formulation and evaluation of colon specific microbial degradable matrir tablet using sterculia gum as carrier"; International Current Pharmaceutical Journal; 1(11); 376-383.
14. Gupta Akhil, Mittal Anuj, Gupta Alok Kumar (2011); "Colon targeted drug delivery system A review"; Russian Jornal of Biopharmaceutics; 3(4); 3-13.
15. Gupta Brahma P., Thakur Navenct, Jain Nishi P., Banweer Jitendra, Jain Surendra (2010); "Osmotically controlled drug delivery system with associated drugs"; J. Pharmaceutical Sci; 13(4); 571-588.
16. Gupta Roop N., Gutpa Rakesh, Dasniwal Pawan k., Rathore Garvendra S. (2014), "Osmotically controlled oral drug delivery- A Reviw"; International Journal of Pharmaceutical Sciences; 1(2); 269-275.
17. Gupta Vinay K., Gnanaraj G., Kothiya Preeti (2012); "A review article on colonic targeted drug delivery system"; The Pharma Journal; 1(7); 14-24.
18. Halsa M, Penttinen T, verki P, Jurjenson H, Marvol M (2001); "Time controlled released pseudoephedrine tablets bioavailability and in vitro/ in vivo correlations"; Pharmazie; 56(9); 718-723.
19. Jain Ashish (2018); "Colon targeting using pH Sensitive material"; Advanced Research in Gastroenterology & Hepatology; 8(5); 1-3.
20. Jain N.K (2001); "Advanes in controlled & novel drug delivery"; CBS publishers and distributors; 1st edition; 86-90.
21. Jain Vikash, Jain Deepika, Raturi Richa, Bansal Praveen, Singh Ranjit (2011); "Recent technologies in pulsatile drug delivery systems"; Bio matter; 1(1); 57-65.
22. Jain Vikash, Shukla Neha, Mahajan SC. (2015); "Polysaccharides in colon specific drug delivery"; open Access text.

23. Jandhyala Sai Mansa, Talukdar Rupjyoti Subramanyam Chivkula, Vayywa Harish, sasikal Mitnala, Reddy D. Nageshwar (2015); "Role of the normal gut microbiota"; World Journal of Gastroenterology; 21(29); Page no- 8787- 8803.
24. Kinget Renaat, Kalala W., Vervoort L, Van Den Mooter G (1998); "Colonic drug targeting"; Journal of Drug Targeting; 6(2); 129 -149.
25. Kolte Bhushan prabhakar, Tele Kalyani V., Mundhe Vinayak S., Lohoti Sandeep S. (2012); "Colon targeted drug delivery system A novel perspective"; Asian Journal of Biomedical and Pharmaceutical Science; 2(14); 21-28.
26. Kumar Amit, Aggarwal Geeta, Harikumar S.L. (2015); "Colon specific drug delivery by Ph Sensitive polymers and pulsatile drug delivery system"; Indo Global Journal of Pharmaceutical Sciences; 5(1); 6-11.
27. Kumar Ravi, Patil M.D, Patil Sachin R., Paschapur Mohesh S. (2009); "Polysaccharieds based colon specific drug deliery : A Review"; International Journal of Pharmtech Research; 1(2); 224-346.
28. Kumar Vipin, Verma Surendra, Mishra D.N., Singh S.K. (2012); "Colon targeted drug delivery: current and novel perspectives"; International Journal of Pharmaceutical Sciences and Research; 3(5); 1274-1284.
29. Malleswari K., Ratna Vijaya (2016); "Colon targeted drug delivery review and novel approaches"; World Journal of Pharmacy and Pharmaceutical Science; 5(5); 1636-1650.
30. Nemade Moheah S, Chaudhari Rajesh Y, Potil Vijay R (2014); "Novel approaches to colon targeted drug delivery system A Review"; Research and Reviews in Pharmacy and Pharmaceutical Science ; 3(2); 63-69.
31. Nugent SG, kumar D., Ramptan DS, Evans DF (2001); "Intestinal luminal pH in inflammatory bowel disease: possible determinants and implications for therapy with amino salicylates and other drugs"; BMJ Journal and GUT; 48(4); 571-577.
32. Padmala Rama krishan Reddy, kondeti Ranjith Reddy, Rajushalem, Mulpuri Kranti Sri (2014); "Colon drug delivery system : A novel perspective"; World Journal of Pharmacy and Pharmaceutical Sciences; 3(9); 212-227.
33. Patel Vipul P, Soniwala Moinuddin M (2012); "Pulsatile drug delivery system for treatment of various inflammatory disorder : A Review"; International Jouranl of Drug Development and Research; 4(3); 67-87.
34. Philip Anil K., Philip Betty (2010); "Colon targeted drug delivery systems a review on primary and novel approaches"; Oman Medical Journal; 25(2); 79-87.
35. Prathap M, Gulshan M.D., Rao N. Rama (2014); "Colon: targeted drug delivery system A Review"; International Jouranl of Research in Pharmaceutical and Nano Sience; 3(5); 429-437.
36. Rajpurohit H, Sharma P, Sharma, Bhandari A (2010); "Polymers for colon targeted drug delivery system"; Indian Journal of Pharmaceutical Sciences; 72(6); 689-969.
37. Rangari Nalanda T, Puranik Prashant K (2015); "Review on recent and novel approaches to colon targeted drug delivery systems"; International Journal of Pharmacy and Pharmaceutical Research; 3(1); 167 - 186.
38. Rao K. Raja, Naik V. Vasu, Rao A. Anka, Rajesh A (2015); " Osmotic controlled drug delivery system: A review"; International Journal of Pharma and Chemical Research; 1(1); page no, 31- 37.
39. Rathod Shruti (2007); "Colon targeted pulsatile drug delivery a review"; Pharma Info Net; 1-11.
40. Ratnaparkhi Mukesh P., Somvanshi Fatte Singh U., Pawar Sham A., Chaudhari Shilpa P, Gupta Jyoti P., Budhavakant Kalyani A (2013); "Colon targeted drug delivery system"; International journal of Pharma Research and Review; 2(8); 33-42.
41. Sears Cynthia L., Garrett wendy S. (2015); "Cell Host & Microbe"; PMC; 15(3); 317-328.
42. Seth Amidon, Brown Jack E., Dave Vivek S. (2015); "Colon targeted oral drug delivery system design trends and approach"; AAPS Pharma SciTech; 16(4); 731-741.
43. Sharma Neha, Harikumar S.L (2013); "Polymer for colon targeted drug delivery system"; International Journal of Drug Development and Research; 5(1); 21-31
44. Singh Amritpal, Sharma Ankush, Pooja, Anju (2014); "Novel approaches for colon targeted drug delivery system"; International Journal of Research and Development in Pharmacy and Life Science ; 3(2); 877-886.
45. Singh Gurmeet, Kumar Dinesh, Singh Mankaran, Sharma Deepak, Kaur Sukhbir (2012); "Emerging techniques and challenges in colon drug delivery system; journal of Applied Pharmaceutical Science; 2(3); 139-147.
46. Singh Nishant, Khanna DR. R.C. (2012); "Colon targeted drug delivery system-A potential approach"; The

Pharma Innovation; 1(1); 40-47.
47. Sirisha V.N.L., Namrata M., Sruthi B., Harika I; Kumar P. Kiran, Rao Y. Kiran Kumar, Pranavi K, (2012); "Pulasatile drug delivery system –A Review; International Jouranl of Pharmaceutical Research and Allied Sciences; 1(3); 13-23.
48. Sreelatha Danda, Brahma Chandan K (2013); "Colon targeted drug delivery- A review on primary and novel approaches"; Journal of Global Trends in Pharmaceutical Sciences; 4(3); 1179-83.
49. Tiwari Gaurav, Tiwari Ruchi, Wal Pranay, Wal Ankita, Rai K. Awani (2010); "Primary and novel approaches for colon targeted drug delivery- A Review; International Journal of Drug Delivery; 2; 01-11.
50. Tuleu C., Andrieux C., Cherbuy C, Darcyvrillon , B., Duee, P.H., Chaumeil, J.C. (2001); "Colonic delivery of sodium butyratevia oral route : acrylic coating design of pellets and in-vivo evaluation in rats"; Methods Find Exp Clin Pharmacol; 23(5); Page no, 245-253.
51. V.V Prasanth, R. Jayabrakash, Mathew Sam (2012); "Colon specific drug delivery system a review on various pharmaceutical approaches"; Journal of Applied Pharmaceutical Sciences; 2(1); 163-69.
52. Vagare Rupali, Doijad Rajendra, Shete Amol, Jagtab Rajesh, Mohit Poonam, Sajane Sachin (2015); "Microbial triggered colon targeted compression coated tablets of tenixicam : formulation and evaluation"; Journal of Drug Delivery and Therapeutics; 5(1); 75-81.
53. Waugh Anne, Grant Allison (2010); "Ross & Wilson Anatomy physiology and pathophysiology in health and illness"; Churchill Livingstone; 11 edition; 297-298.