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# REVIEW ON: COLON TARGETED DRUG DELIVERY SYSTEM

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## ABSTRACT

The colon is the terminal part of the GIT which has gained in recent years as a potential site for delivery of various novel therapeutic drugs, i.e. peptides.colon targeted drug delivery system (CDDS) is an promising tool for local treatment of variety of bowel disease ulcerative colitis systemic delivery of protein and peptide.This review is focused on the potential opportunities and challenges available in novel area of colon targeted drug delivery system. New systems and technologies have been developed for colon targeting and to overcome pervious method's limitations. Colon targeting holds a great potential and still need more innovative work. This review article discusses, in brief, introduction of colon along with the novel and emerging technologies for colon targeting of drug molecule.

**KEYWORDS:** colon targeted, bowel disease, protein and peptides.

## INTRODUCTION[1]

The oral aspect is considered to be most convenient for administration of drugs to Patients. Normally dissolves in stomach field as intestinal fluid and absorb from these regions of GIT. It is a serious drawback in conditions when localized delivery of drugs into the colon is required as drugs needs to be protected from the hostile environment of upper GIT. Targeted drug delivery into the colon is highly desirable for local treatment of variety of bowl diseases such as ulcerative colitis, cirrhosis disease, amoebiasis, colonic cancer, local treatment of colonic pathologies and systemic delivery of protein andpeptide drugs. The colon specific drug delivery system (CDDS) should be capable of protecting the drug in route to the colon i.e. drug release and absorption should not occur in stomach as well as small intestine, and

neither the bioactive agent should be degraded either of the dissolution sites, but only released absorbed once the system reaches the colon.

Formulations for colonic delivery are also suitable for delivery of drugs, which are polar and / or susceptible to chemical and enzymatic degradation in upper GIT; in particular, therapeutic proteins and peptides are suitable for colonic deliveries. Proteins and peptides such as insulin, calcitonin and vasopressin may be delivered systematically via colonic absorption. Other examples include novel peptides such as cytokine inhibitors and antibiotics, which are useful in treatment of IBD and GI infections respectively.

**Advantages of CDDS over conventional drug delivery[8]**

1. Chronic colitis, namely ulcerative colitis and cirrhosis disease are currently treated with glucocorticoids, and other anti-inflammatory agents.
2. Drugs are available directly at the target site.
3. Side effects can be reduced.
4. Utilization of drug is more and lesser amount of dose is required comparatively.

**Disadvantages[6]**

a) Low dose loading
b) Higher need of excipients
c) Lack of manufacturing Reproducibility and efficacy
d) Multiple formulation steps
e) Large number of process variables
f) Need of advanced technology.
g) Skilled personal needed for Manufacturing of colonic drug delivery system.

**Need of colon targeted drug delivery[8,9]**

1. Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects.
2. Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery.
3. Colon-specific drug delivery system is considered to be beneficial in the treatment of colon diseases.

4. The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine (targeted).
5. A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon.

**Limitations of colon targeting drug delivery System[2,5]**

1) Multiple manufacturing steps.
2) Incomplete release rate.
3) The resident microflora could also affect colonic performance via metabolic degradation of the drug.
4) Non availability of an appropriate dissolution testing method to evaluate the dosage form in vitro.
5) Bioavailability of drug may be low due to potentially binding of drug in a nonspecific way to dietary residues, mucus or fecal matter.

**Drugs used in colon cancer[2]**

a) 5-fluorouracil
b) 9-aminocamptothecin
c) Capecitabine
d) Cetuximab
e) Trinotecan
f) Levamisole hydrochloride
g) Oxaliplatin
h) Trimetrexate
i) UFT (ftorafur and uracil)
j) Bevacizumab,

**Anatomy and Physiology of Colon[3,6,7,12,17]**

The GI tract is divided into stomach, small intestine and large intestine. The large intestine extending from the ileocecaljunction to the anus is divided in to three main parts. These are the 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 coloncontain the left half of the transversecolon, descendingcolon, splenic flexure and sigmoid. The rectum is the last anatomic segment before the anus. The human colon were shown in Figure1.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 capacity is very high, each about 2000ml of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed.(Fig: 1)

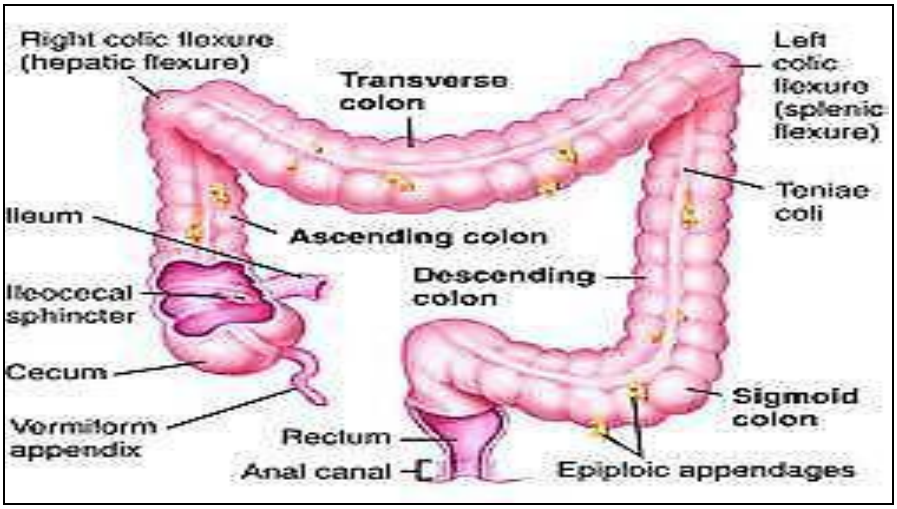


**Fig 1: Anatomy of colon.**

**Table no.:-1 Criteria for selection of drugs for CDDS[4,11]**

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

**Newly Developed Approaches for Cdds[12]**

**Novel colon targeted delivery system (CODES TM)**

CODESTM was a unique CDDS technology which is a combined approach involving pH dependent and microbiology triggered CDDS and was designed to avoid the inherent problems associated with pH or time dependent systems. It was developed by utilizing a unique mechanism involving lactulose, acting as a trigger for site specific drug release in the colon.The system consists of a traditional tablet core containing lactulose, which is coated with acid soluble material Eudragit E, and then subsequently over coated with an enteric material, Eudragit L. The final conclusion of this 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 will 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 thus cause subsequent drug release.

**Osmotic Controlled Drug Delivery (ORDS-CT)[12]**

The OROS-CT was used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable. The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 units, each encapsulated within a hard gelatin capsule. Each bilayer unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane thus it is called as a push-pull unit. Immediately after the OROS-CT is swallowed, the gelatin capsule containing the pushpull units dissolves. Each push-pull unit was prevented from absorbing water in the acidic aqueous environment of the stomach, and hence no drug is delivered because of its drug impermeable enteric coating. As the unit enters the small intestine, the coating dissolves because of higher pH environment (pH >7) water enters the unit causing the osmotic push compartment to swell and concomitantly creates a flowable gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice in a rate controlled manner. Various in-vitro/in-vivo evaluation techniques have been developed and proposed to test the performance and stability of CDDS.

**Combination of Different Approaches of CDDS[12]**

An oral colonic drug delivery system of 5-aminosalicylic acid was developed using combination of pH dependent, time-based and enzyme degradable approaches. The pellets were coated with three functional layers i.e. the outer EudragitL30D-55 layer for protection against GI fluids, the intermediate layer of ethyl cellulose to inhibit the drug release during passage through the small intestine and the inner layer of pectin for swelling and enzyme degradation. In-vitro release studies indicated that the coated pellets completely protected the drug release in 0.1M HCl while the drug release was delayed for 3 to 4 h in pH 6.8 phosphate buffer. Pulsatile device was formulated to achieve time or site specific release of theophylline based on chronopharmaceutical consideration. The basic design consists of an insoluble hard gelatin capsule body filled with Eudragit microcapsules of theophylline and sealed with a hydrogel plug and finally the enteric device was enteric coated. In this approach, pH sensitive and time dependent delivery systems were combined. In this the thickness of enteric coat is a measure of protection from stomach and intestine pH. Different hydrogel polymers were used as plugs to maintain a suitable lag period. The hydrophilic polymer content is a measure of delayed release of theophylline from microcapsules.

**Hydrogel based CDDS[8]**

Hydrogels are usually formed by the covalent crosslinking of linear hydrophilic polymers to form a network of material capable of absorbing water, yet still remaining insoluble. Heterogenous polymer mixture may also be used to form hydrogels without the need for covalent crosslinking .Glutaraldehyde cross-linked dextran capsules were prepared for colon specific delivery. Along with magnesium chloride and PEG 400 in water the capsule caps and bodies were prepared on nylon molding pins. Then the dextran capsules were filled with model drug (Hydrocortisone) and drug release was studied. The drug release pattern was suitable for colon targeting. The hydrogels formed by cross-linked polyvinyl alcohol were suitable for colon specific drug delivery systems. In this method polyvinyl alcohol of different molecular weights was cross-linked with succinyl, adipoyl, or sebacoyl chloride to obtain hydrogel-forming polymers. The hydrophilic drugs like diclofencac sodium, propranolol hydrochloride and vitamin B6 hydrochloride were used as model drugs. A new microparticulate system containing budesonide.

**Pulsincap system**[12,13,14]

Single-unit systems are mostly developed in a capsule form. The lag time is controlled by a plug, which gets pushed away by swelling or erosion and the drug is released as a "Pulse" from the insoluble capsule body. One such system comprises of a waterinsoluble capsule enclosing the drug reservoir. A swellable hydrogel plug was used to seal the drug contents into the capsule body60. When this capsule comes in contact with the dissolution fluid, it swelled and after a lag time, the plug pushed itself outside the capsule and rapidly released the drug. Polymers used for the hydrogel plug were different viscosity grades of hydroxypropyl methyl cellulose (HPMC), poly methyl methacrylate, polyvinyl acetate and poly ethylene oxide. The length of the plug and its point of insertion into the capsule controlled the lag time.

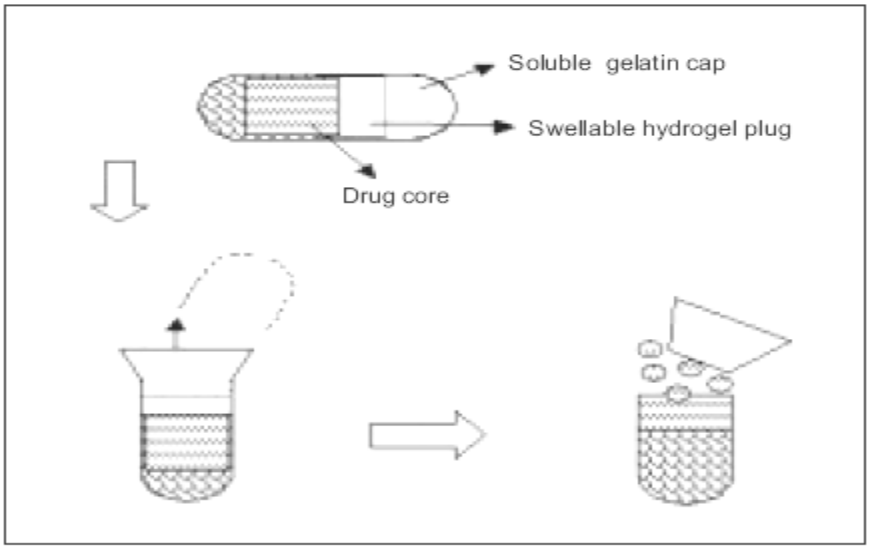


**Fig. 2: Design of Pulsincap system.**

**Port System**[1314]

The Port system consists of a capsule coated with a semipermeable membrane. Inside the capsule was an insoluble plug consisting of osmotically active agent and the drug formulation. When this capsule come in contact with the dissolution fluid, the semipermeable membrane allow the entry of water leading to the pressure development inside the capsule and the insoluble plug expelled after a lag time (Fig.3). The dosage form is designed in such a manner that upon ingestion, the first drug release pulse occurs within 1-2 h, followed by period during which no release occurs. Second dose is released in 3-5 h of ingestion. This is again followed by asecond no-release interval. Release of third dose occurs within 7-9 h of ingestion. This system avoids the second time dosing.

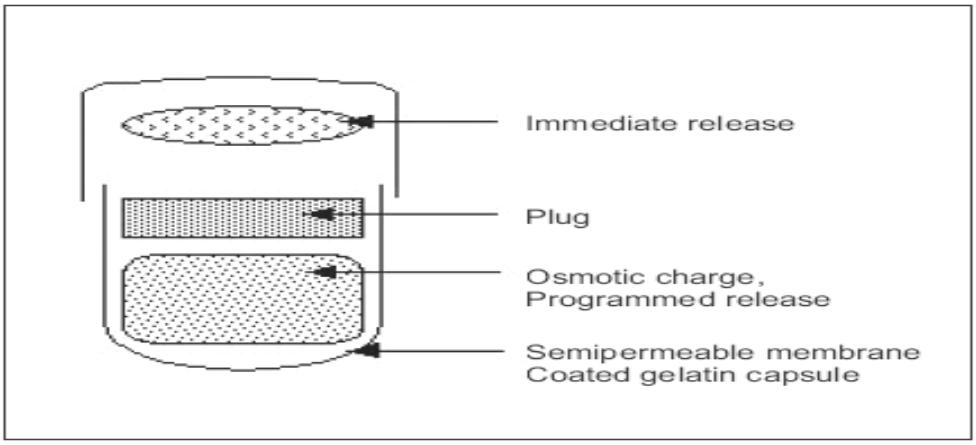


**Fig. 3: Plan of Portsystem.**

In the pulsatile drug delivery systems (PDDS), the release of an active molecule within a short time period is rapid and transient and can be produced immediately after a predetermined off release period. The approach is based on the principle of delaying the time of drug release until the system transits from mouth to colon. The transit time of small intestine is about 3-4 hours so lag-time of 5 hours is usually considered, which is relatively constant and hardly affected by the nature of the formulation administered. Recently considerable attention has been focused on the development of PDDS. Oral route of drug delivery is generally preferred as drug release rate can be varied. The drug release in these system generally occurs within therapeutic window for prolong period of time and hence these systems show sustained release of drug from dosage form.

**Advantages of PDDS are**

1. Extended daytime or nighttime activity
2. Reduced side effects
3. Reduced dosage frequency
4. Reduction in dose size
5. Improved patient compliance
6. Lower daily cost to patient due to fewer dosage units are required by the patient in therapy.
7. Drug adapts to suit circadian rhythms of body functions or diseases.
8. Drug targeting to specific site like colon.
9. Protection of mucosa from irritating drugs.
10. Drug loss is prevented by extensive first pass metabolism.

**CODESTM technology**[12,13,14]

To avoid the inherent problems associated with pH- or time dependent systems the CODESTM technology was designed for colon-specific drug delivery. The CODESTM technology having advantages of certain polysaccharides that are only degraded by bacteria which are available in the colon that could be coupled with a pH-sensitive polymer coating. These systems exhibited the capability to achieve colon delivery consistently and reliably as the polysaccharides degradation mainly occur in the colon. One typical configuration of CODESTM consists of a core tablet coated with three layers of polymer coatings as schematically presented in Fig 4.

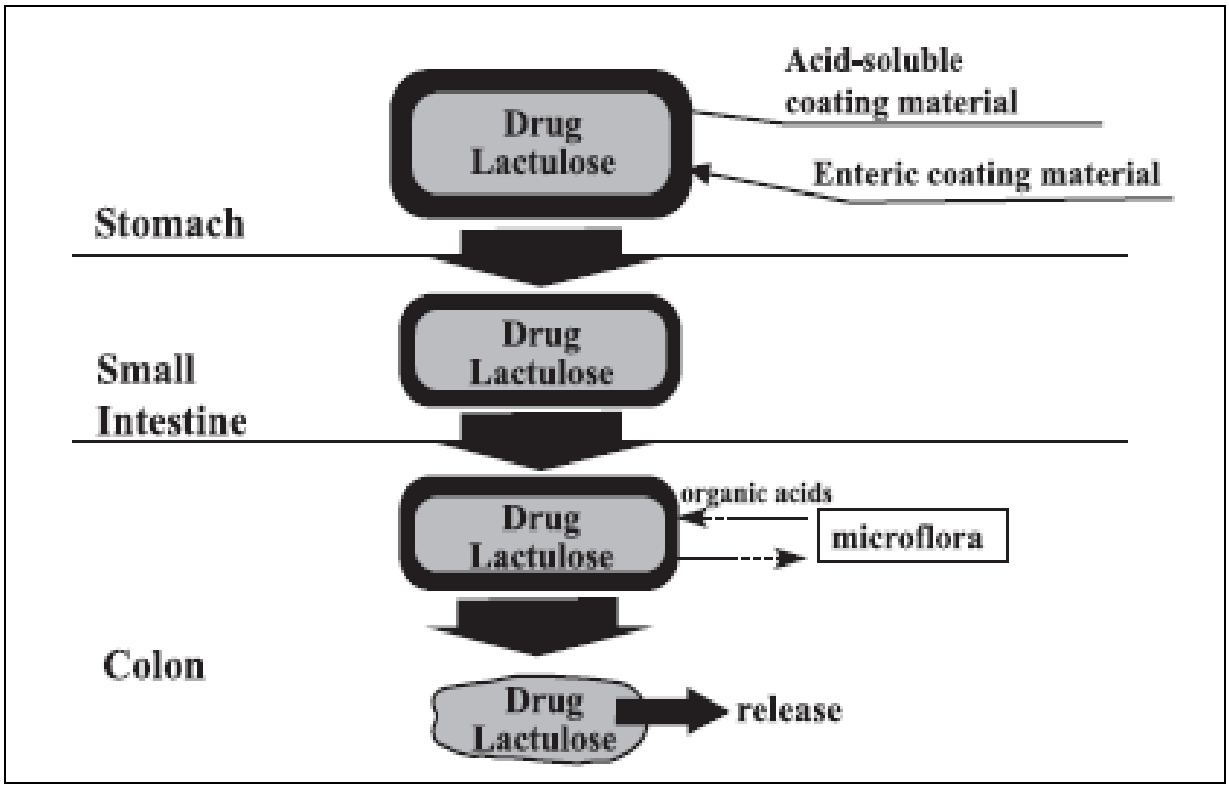


**Fig 4: Schematic of the CODESTM formulation82**

**Osmotically controlled system (ORDS- CT)**[12,13,14

The OROS-CT (Alza corporation) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule, Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semi permeable membrane. An orifice is drilled through the membrane next to the drug layer (Fig.5). Immediately after the OROS-CT is swallowed, the gelatin capsule containing the

push-pull units dissolves. Because of its drug-impermeable enteric coating, each push-pull unit is prevented from absorbing water in the acidic aqueous environment of the stomach, and hence no drug is delivered. As the unit enters the small intestine, the coating dissolves in this higher pH environment (pH >7), compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semi permeable membrane. For treating ulcerative colitis, each push pull unit is designed with a 3-4 h 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 hours in the colon or can deliver drug over a period as short as four hours. Recently, new phase transited systems have come which promise to be a good tool for targeting drugs to the colon. Various in-vitro/in-vivo evaluation techniques have been developed and proposed to test the performance and stability of CDDS. GI pressure is another mechanism that is utilised to initiate the release drug at distal part of GUT.

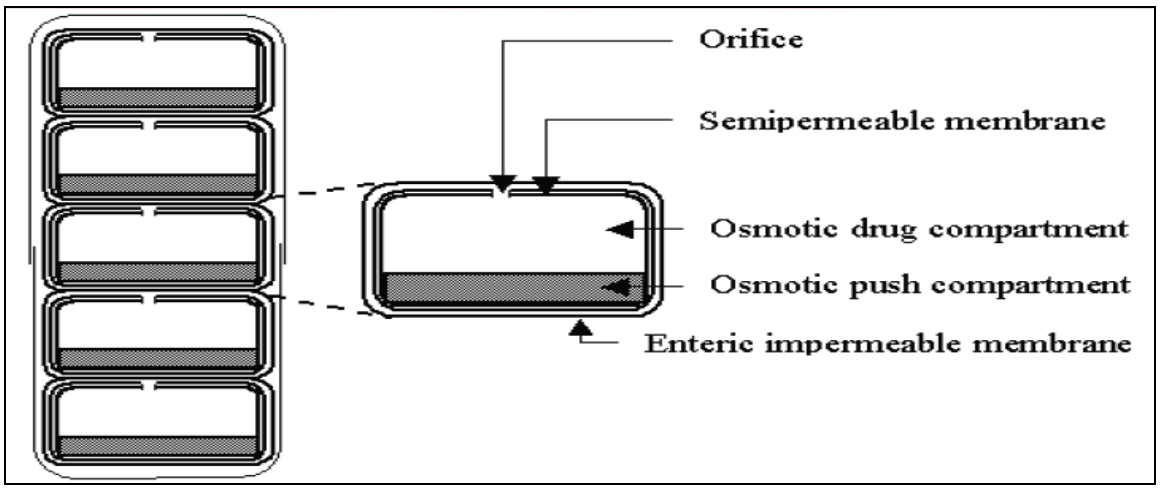


**Fig.5. Osmotically controlled system**

**Approaches Used For Site Specific Drug Delivery To Colon[9]**

Several approaches are used for site-specific drug delivery. Among the primary approaches for CDDS, These include.

**Primary approaches of colon specific drug delivery system[9]**

**1. PH- dependent delivery[9]**

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.

**Table no:-2 Marketed PH Dependent System[15]**

| Drug used in Disease | Polymer used | Dosage form | Disease |
|---|---|---|---|
| Tegasrod maleate | Eudrajit L100, Eudrajit S100 | Tablet | Irritable bowel syndrome |
| Prednisolone | Eudrajit L100, Eudrajit S100 | Tablet | Ulcerative colitis |

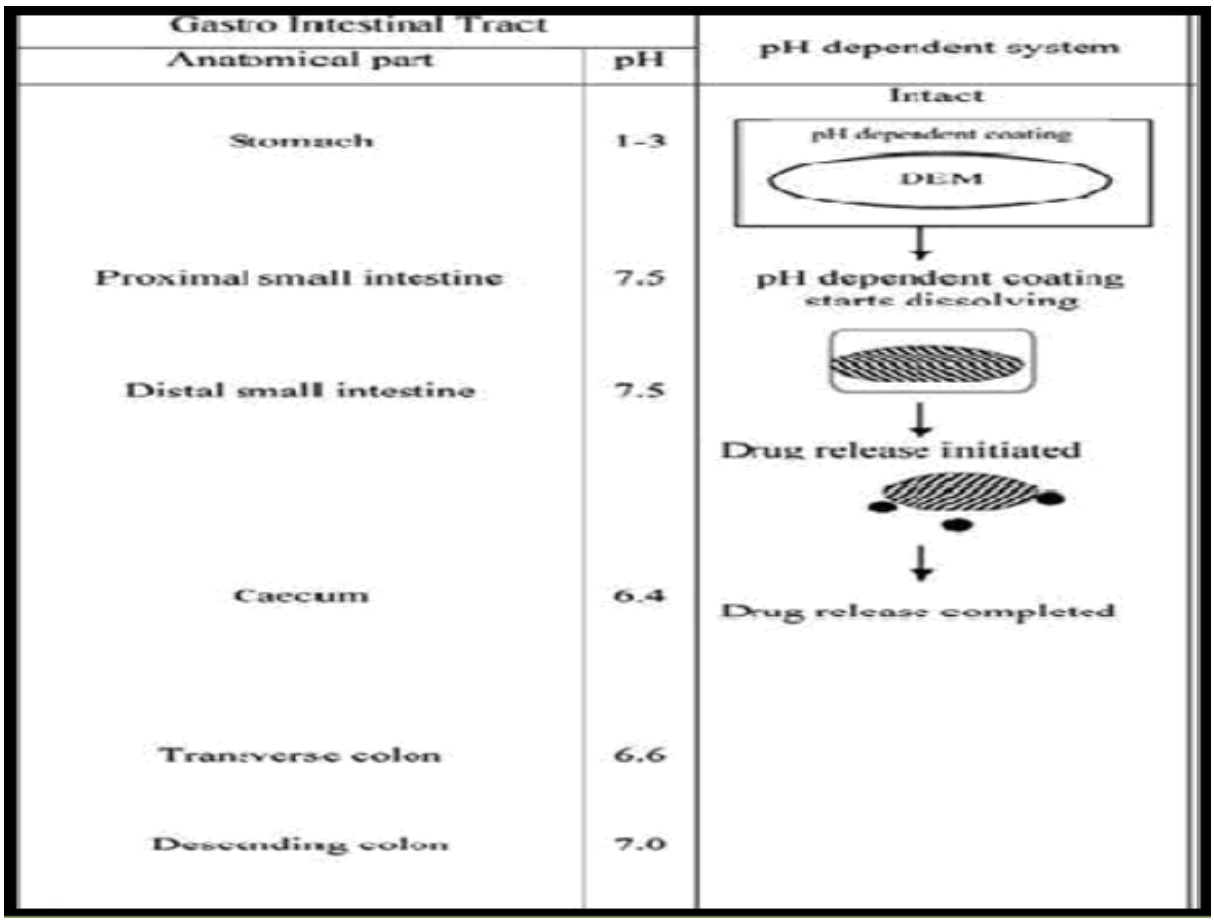


**Fig:-6 PH- dependent delivery**

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.

**2. Time dependent delivery system[9,11]**

Time dependent/controlled release system (TCRS) such as sustained or delayed release dosage forms are also very promising drug release systems. However, due to potentially large variations of gastric emptying time of dosage forms in humans, in these approaches, colon arrival time of dosage forms cannot be accurately predicted, resulting in poor colonical availability. Time dependent systems are not ideal to deliver drugs to the colon specifically 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. Since the transit time of dosage forms in the small intestine is less variable i.e. about 3±1 hr. The time-release function (or timer function) should work more efficiently in the small intestine as compared the stomach. In the small intestine drug carrier will be delivered to the target side, and drug release will begin at a predetermined time point after gastric emptying. On the other hand, in the stomach, the drug release should be suppressed by a pH sensing function (acid resistance) in the dosage form, which would reduce variation in gastric residence time. Enteric coated time-release press coated (ETP) tablets, are composed of three components, a drug containing core tablet (rapid release function), the press coated swellable hydrophobic polymer layer (Hydroxy propyl cellulose layer (HPC), time release function) and an enteric coating layer (acid resistance function). The tablet does not release the drug in the stomach due to the acid resistance of the outer enteric coating layer. After gastric emptying, the enteric coating layer rapidly dissolves and the intestinal fluid begins to slowly erode the press coated polymer (HPC) layer. When the erosion front reaches the core tablet, rapid drug release occurs since the erosion process takes a long time as there is no drug release period (lag phase) after gastric emptying. The duration of lag phase is controlled either by the weight or composition of the polymer layer (HPC), (Fig. 7).

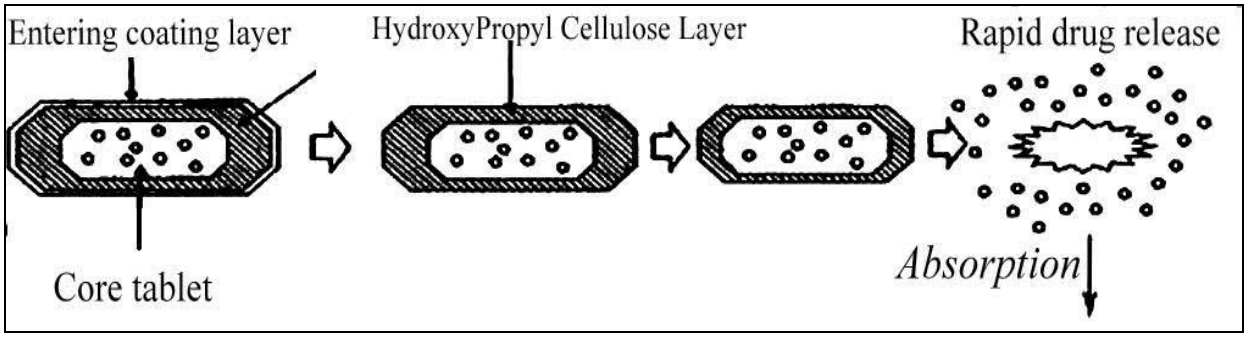


**Fig:-7 Design of enteric coated timed-release press coated tablet (ETP Tablet).**

### 3. Microbially triggered system[12,15]

The basic principle involved in this methodis degradation of polymers coated on the drugdelivery system by microflora present in colon and there by release of drug load in colonicregion because the bio environmentinside the human GIT is characterized by presence ofcomplex microflora, especiallythe colon is rich in microorganisms. In this method, drugsand/or dosage forms are coated with the biodegradable polymers i.e., the polymers degradedue to influence of colonic microorganisms. When the dosage form passes through the GIT, itremains intact in the stomach and small intestine where very little microbial degradableactivity is present which is insufficient for cleavage of the polymer coating.This approach isdifferent from probiotic approach because in probiotic approach, we are providing microflorafrom external source which assist the interior flora.

**Table no:- 2 Microbial Triggered based polymer for various drugs.**

| Sr. No. | Polymers used | Drug used |
|---|---|---|
| 1 | Chitosan | Diclofenac sodium |
| 2 | Pectin | Indomethacin |
| 3 | Guar gum | 5-Flourouracil |
| 4 | Chondroitin Sulphate | Indomethacin |
| 5 | Amylose | 5-Acteyl salicylic acid |

### 4. Pressure-controlled drug-delivery systems[14]

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine, have developed pressure controlled colon-delivery capsules prepared using ethyl cellulose, which is insoluble in water. In such systems drug release occurs following disintegration of a water-insoluble polymer capsule as a result of pressure in the lumen of the colon. The thickness of the ethyl cellulose membrane is the most important factor for disintegration of the. The system also appeared to depend on capsule size and density. Because of reabsorption of water from the colon, the viscosity of luminal content is higher in

the colon than in the small intestine. It has therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems. In pressure-controlled ethyl cellulose single-unit capsules the drug is in a liquid. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to human.

**Evaluation of Colon- Specific Drug Delivery Systems[12,16]**

**Different in vitro and in vivo methods[12,16]**

Different in vitro and in vivo methods are used to evaluate different carrier systems for their ability to deliver drugs specifically to the colon. The ability of the coats or carriers to remain intact in stomach and small intestine is generally assessed by conducting drug release studies in 0.1N hydrochloric acid for 2 hours followed by phosphate buffer (pH -7.4) for 3 h by using dissolution apparatus. The drug release studies may also be performed by using rat cecal contents.

Another in-vitro method involves incubation of the drug delivery system in a fermentor with commonly found colonic bacteria. In vivo methods offer various animal models. Guineapigs were used to evaluate colon- specific drug delivery from a glucoside prodrug of dexamethasone. In vivo gamma scintigraphic studies were carried out on the guar gum matrix tablets, using technetium 99 m- DTPA as a tracer. Scintigraphs taken at regular intervals have shown that some amount of tracer present on the surface of the tablets was released in stomach and small intestine. Radiotelemetry, Roentenograpgy are the other in vivo evaluation methods for colon-specific drug delivery systems.

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