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REVIEW ARTICLE: CONVENTIONAL & NOVEL APPROACHES FOR COLON DRUG DELIVERY SYSTEM

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ABSTRACT
Colon targeted drug delivery system (CDDS) helps in treatment of wide range of local diseases like ulcerative colitis, crohns diseases, irritable bowel syndrome, chronic pancreatitis, colorectal cancer and also help in treating non- colonic condition as colon act as potential site for systemic absorption of several drugs . This article reveals need, advantage, problems of colon targeted drug delivery .Further review article provide a discussion on primary approaches including Transit time dependent, pH dependent, bacterial enzyme dependent colonic drug delivery system, pH & Time dependent DDS, pH & bacterial enzyme DDS. Newer approaches like colonic pressure controlled CDDS, Osmotic pressure controlled CDDS, Pulsatile colonic drug delivery system.

KEYWORDS: CDDS, Eudragit, Transit Time, Lag Phase, Colonic Micro-flora.

INTRODUCTION

Colon targeted drug delivery has gained increased importance & is relatively recent approach for treatment of diseases like ulcerative colitis, crohns disease, colorectal cancer and amoebiasis. Colon specific delivery system are also gaining importance for its potential for the delivery of proteins and Therapeutic peptides like insulin, minimizes the extensive first pass metabolism of steroids and produces delay in absorption of drug to treat rheumatoid arthritis, angina. Different approaches are designed to develop colonic drug delivery system.

Anatomy & physiology of colon[3]

Gastrointestinal Tract (GIT) is divided into stomach, small intestine, large intestine. The large intestine extends from ileocecal junction to anus. Large intestine is divided into three main parts colon, rectum and anal canal. The entire colon is about five feet long (150 cm).

Colon can be divided into right & left colon

Right Colon: 1) Cecum 2) Ascending Colon 3) Hepatic Flexure 4) Right Half of Transverse Colon.
Left Colon: 1) Left Half of Transverse Colon 2) Descending Colon 3) Splenic Flexure 4) Sigmoid.

The wall of colon consists of 4 layer's Serosa, Muscularis externa, Submucosa, Mucosa.
The Serosa is exterior coat of large intestine and is composed of areolar tissue that is covered by squamous mesothelial cells. Muscularis externa is major muscular coat of large intestine and is composed of inner circular layer of fibre that surrounds the bowel and of an outer longitudinal layer.The Submucosa lies immediately beneath the mucosa and is made up of connective tissue . Mucosa lines the lumen of colon and is made up of epithelium, lamina propria and Muscularis mucosa. Muscularis mucosa made up of layer of smooth muscle and separates the submucosa from lamina propria.Lamina propria supports epithelium and occupies space between the crypts and beneath crypts.

Lamina propria consists of blood vessels, lymphatic lacteals. The epithelium consists of single layer of cells which lines the crypt and covers the surface of mucosa. Three major type of cells found in columnar absorptive cells, goblet cells (mucous cell, enteroendocrine cells. Mucus production in colon is function of goblet cells and proportion of goblet cells increase in elderly. The superior mesenteric artery supply blood to proximal colon and inferior mesenteric artery supply blood to distal colon.

Physiology of GIT is complex has wide range of pH & Transit time.

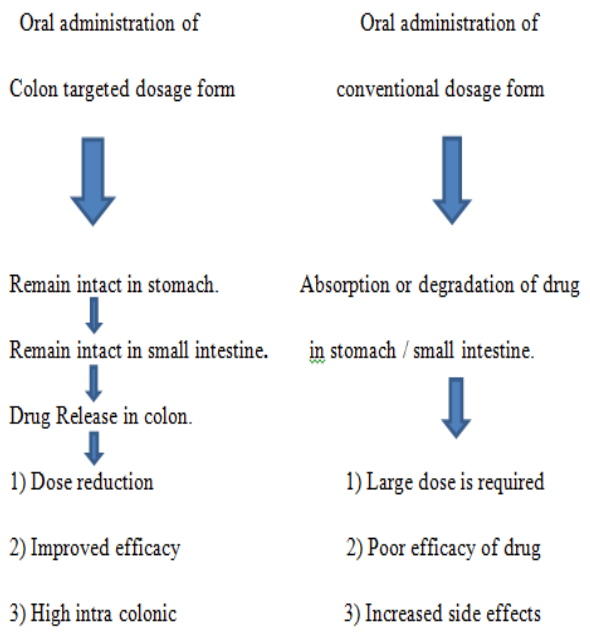
Organ	pH	Transit Time
A) Stomach		
1) fasted state	1.5 – 2	10 min - 2 hrs.
2) Fed state	2-6	> 2 hrs.
B) Small intestine	6.5-7.5	3-4 hrs.
C) Colon		20-30 hrs.
1) Ascending colon	6.4	
2) Transverse colon	6.6	
3) Descending colon	7	

Colon serves following functions

1) Storage reservoir of faecal contents.
2) To secrete K^+ & HCO_3^-.
3) Expulsion of contents of the colon at an appropriate time.
4) Absorption of sodium & water.

Need of colon specific drug delivery

1)Failure of conventional drug delivery system used in treatment of colonic disorder due to inadequate amount of drug reaching the site of action thus resulting in poor efficacy of drug.



Concentration

2) Promising drug delivery system for proteins, peptides & vaccines.

Advantages of colon targeted drug delivery

1) Drug directly reaches the targeted site.
2) Reduce dose frequency.
3) Efficient delivery of proteins, peptides & vaccines.
4) Colon has long retention time, causes increase in absorption of Drug.
5) Avoid first pass metabolism.
6) Improve patient compliance.
7) proper utilization of drug.

Problems in colon targeted drug delivery

1) Dosage form that is orally administered has to traverse the entire alimentary canal in order to reach target site (colon).
2) Physiology of GIT is complex has wide range of pH values, fluid volumes and transit time.
3) Presence of low colonic luminal fluid volume, higher viscosity, neutral pH.

Properties of drug candidate for colon specific drug delivery

1) Drug that show poor absorption from stomach & intestine.
2) Drug that are degraded or inactivated in stomach / small intestine due to acidic environment of stomach & pancreatic enzymes in small intestine.
3) Drug that undergo extensive first pass metabolism.
4) Drug should be stable at alkaline pH of GIT.

Criterion for selection of Carrier for CDDS.

1) Carrier selection for CDDS depends on
a) Nature of drug b) Disease for which drug is used.
2) The various physico-chemical factors of drug need to be while selections of carrier are as follows:
a) Chemical nature b) stability c) Partition Coefficient

Polymers used in CDDS: Mainly two types of polymers is used natural & synthetic, using these polymers controlled drug delivery is achieved.[8,10,15]

Natural Polymers	Synthetic polymers
1) Pectin	Eudragit L 100
2) Chondroitin Sulphate	Eudragit S 100
3) Dextran	Eudragit L 30D
4) Cyclodextrin	Eudragit RS 30D
5) Amylose	Polyvinyl acetate phthalate
6) Chitosan	Hydroxy Propyl ethyl cellulose
7) Guar Gum	Hydroxy Propyl ethyl cellulose 50
8) Xanthum Gum	Hydroxy Propyl ethyl cellulose 55
9) starch	Cellulose acetate phthalate
10) Locust bean Gum	Cellulose acetate trimellitate

Polymethacrylate polymer like Eudragit L 100, Eudragit S 100 are used in pH dependent colonic drug delivery system. Eudragit L 100: Enteric coating resistant to gastric fluid becomes soluble in intestinal fluid from pH 6. Eudragit S 100: Enteric coating resistant to gastric fluid becomes soluble in intestinal fluid from pH 7. Eudragit L 30D: Enteric coating resistant to gastric fluid becomes soluble in intestinal fluid from pH 5.6 Polymers that are polysaccharide in nature eg Pectin, Guar Gum, Chitosan remain intact in stomach & small intestine are degraded by colonic microflora to simple saccharides thus such polymers are used in Bacterial enzyme dependent colonic drug delivery system. Chondroitin Sulphate is soluble mucopolysaccharide that is degraded by B. Ovatus, B. Thetalotaomicron in large intestine. Dextran is degraded by microbial enzyme Dextranases which is found in colon.Amylose is fermented by amylose in colon.Inulin is fermented by Bifidobacteria present in colon. Cyclodextrin, in colon they undergo fermentation in presence of vast colonic microfloras into small monosaccharide's.

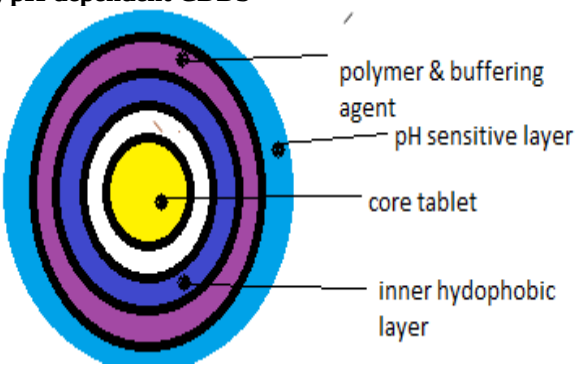
Approaches for colon drug delivery system (CDDS)
1) Transit time dependent CDDS.
2) pH dependent CDDS.
3) pH & time dependent CDDS.
4) Bacterial enzyme dependent CDDS.
a) Prodrug based System.
b) Azo Prodrug.
5) pH & Bacterial enzyme dependent CDDS.
6) Colonic Pressure controlled DDS.
7) Osmotic Pressure controlled CDDS.
8) Pulsatile colon targeted DDS.
a) Pulsincap system.
b) Port system.

1) Transit time dependent CDDS[1,2]
The drug is released after a pre-programmed time delay.To obtain release in colon, the lag time should equate to the time taken for the system to reach the colon.Colon arrival time of dosage form cannot be accurately predicted, although lag time of five hours is considered sufficient. The most current time release system consists of use of outer enteric coat along with inner polymeric barrier.The outer enteric coat dissolves on entering small intestine to reveal inner polymeric barrier which delays drug release by swelling, eroding or dissolving over period time equivalent to small intestinal transit.

- **Disadvantage**

1) Gastric emptying time varies between subjects .Gastric emptying time varies with type and amount of food intake.
2) Gastrointestinal transit is prone to diurnal rhythms with transit being appreciably slower in evening as compared with morning.
3) Time at which the dosage form reaches colon cannot be predicted accurately resulting in poor colonic bio-availability of drug.

2) pH dependent CDDS[4,5]

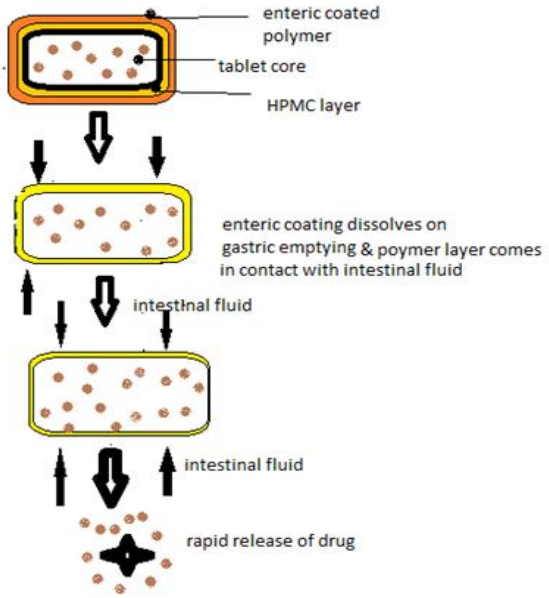


The coating of pH sensitive polymer to dosage form (Tablet, capsule, pellets) provide delay release and protect the active drug from gastric fluid.pH dependent polymer used for colon targeting should withstand pH values of stomach, small intestine and should disintegrate in neutral of slightly alkaline pH of terminal ileum.Gamma Scintigraphy most popular method to investigate gastrointestinal performance of pharmaceutical dosage form.

- **pH dependent polymers and their Threshold pH.[15]**

Polymer	Threshold pH
Eudragit L 100	6
Eudragit S 100	7
Eudragit L 30D	5.6
Polyvinyl acetate phthalate	5.0
HPMC phthalate	4.8
HPMC phthalate 50	5.2
HPMC phthalate 55	5.4
Shellac	7.0

3) pH & Time dependent colon DDS.[12]



The time taken by formulation to leave the stomach varies greatly and transit time through small intestine is independent of formulation.pH & Time depedent CDDS was developed to minimize the effect of variation of gastric residence time.The system include Core tablet surrounded by two layers:1) swellable hydrophobic polymer layer 2) enteric coating layer.The enteric coating layer prevent release of drug in stomach, the enteric coating layer dissolves on gastric emptying . Hydrophobic swellabe polymer comes in contact with intestinal fluid and erodes the polymer.When the erosion front reaches the core tablets, rapid drug release occur.Lag Phase can be controlled by molecular weight or composition of the polymer.

4) Bacterial enzyme dependent CDDS.[7]
a) Prodrug based system: Prodrug is inactive moiety which undergoes enzymatic transformation to release the active parent drug. e.g. sulphasalazine used in inflammatory bowel disease is prodrug on which azoreductase (enzyme) acts to release 5-ASA (5-Amino salicylic acid) which is active parent drug .Prodrug is formed by linking the active parent drug to hydrophobic carrier like amino acids, glucose,

galactose,cellulose.Prodrug are hydrolysed in presence of enzymes released by microflora.Drawback – Formulation depends on the functional group available on drug moiety for chemical linkage.

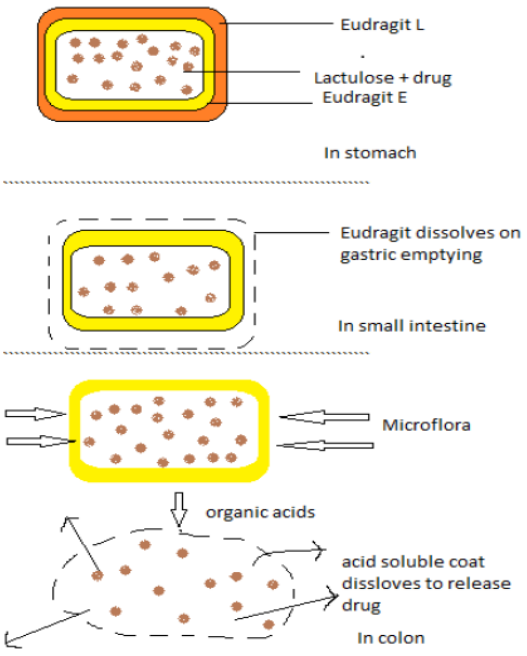
- **Example of prodrug system for CDDS**

Drug	Carrier	Linkage hydrolysed
5-ASA	Azo Carrier	Azo linkage
Dexamethasone	Saccharide Carrier	Glycosidic linkage
Prednisolone	Glucose	Glycosidic linkage
Salicylic acid	Aminoacid Conjugate, glycine	Amide linkage

b) Azo Prodrug

In this approach there is breakdown of linkage bond between & Carrier by reduction and hydrolysis by enzymes from colon bacteria.Typical enzymes include glycosidase, azoreductase and glucuronidase.Sulphasalazine was used in treatment of rheumatoid arthritis was later known to be potential in treatment of inflammatory bowel disease.Sulphasalazine is 5-Amino salicylic acid (5-ASA) coupled with sulphapyridine by azo bonding on reaching colon azo bond is reduced by enzyme azoreductase to 5-Amino salicylic acid and sulphapyridine.5-ASA is active parent drug & sulphapyridine is carrier molecule to deliver 5-ASA intact to colon .Many side effects of sulphasalazine is only due to systemic absorption of sulphapyridine from colon.Olsalazine consist of two 5-ASA molecules linked by azo bond was developed to deliver 5-ASA to colon without use of sulphapyridine.

5) pH and bacterial enzyme dependent CDDS.[13]



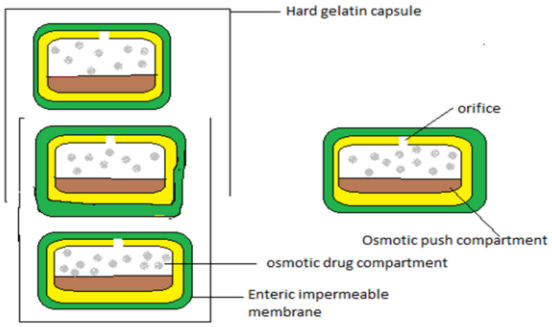
In this approach the system consist of core tablet containing Lactulose which is coated with acid soluble material Eudragit E which is again overcoated with Eudragit L.Enteric coating protect tablet while in the stomach, dissolves quickly following gastric emptying.Acid soluble substance protect as the tablet passes through small intestine.As the tablet arrives colon, bacteria enzymatically degrade lactulose. Eudragit L 100 - soluble in intestinal fluid from pH 6, Eudragit S 100 - soluble in intestinal fluid from pH 7.Eudragit E - Acid soluble material.Lactulose is fermented by colonic bacteria to produce large amount of lactic acid result in drop of pH to about pH 5.Organic acids produce dissolves acid soluble coat to release drug.

6) Colonic pressure controlled DDS.[13]

Takaya et al (1995) - Capsule made up of insoluble ethyl cellulose was developed for colonic pressure controlled DDS.In this system the drug release occur after the disintegration of water insoluble ethyl cellulose capsule.System depends on: 1) Thickness of ethyl cellulose membrane. 2) System was found to depend on density & Capsule size.

Drawback: Due to reabsorption of water from the colon, the viscosity of luminal content of colon is higher than small intestine thus drug dissolution in colon could be problem to colon specific drug delivery system.The drug is given in liquid form, lag times of 3-5 hours in relation to drug absorption were noted when pressure controlled capsule was administered to human.

7) Osmotic pressure controlled CDDS

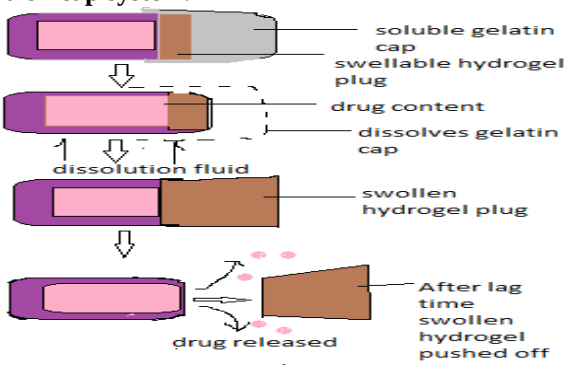


In this approach the system consist of single osmotic unit or many push -pull units encapsulated by hard gelatin capsule.Each push-pull unit consist of two layers, outer enteric impermeable membrane & inner semi-permeable membrane with orifice. Core of Push- Pull unit consist of osmotic drug compartment & osmotic push compartment containing osmotic agent.The gelatin capsule dissolves immediately after swallowing the capsule.The impermeable membrane prevents absorption of water from acidic aqueous environment in stomach.To prevent drug release in small intestine push pull units are designed with 3-4 hrs post gastric delay.Enteric coating dissolves at higher pH (pH >7). Water from intestinal fluid passes into push pull unit & causing push

compartment swells and exert pressure on drug compartment leading to drug release through orifice in colon.The drug released from push pull unit is osmotically / osmotic controlled i.e. amount of water entered into push pull units.

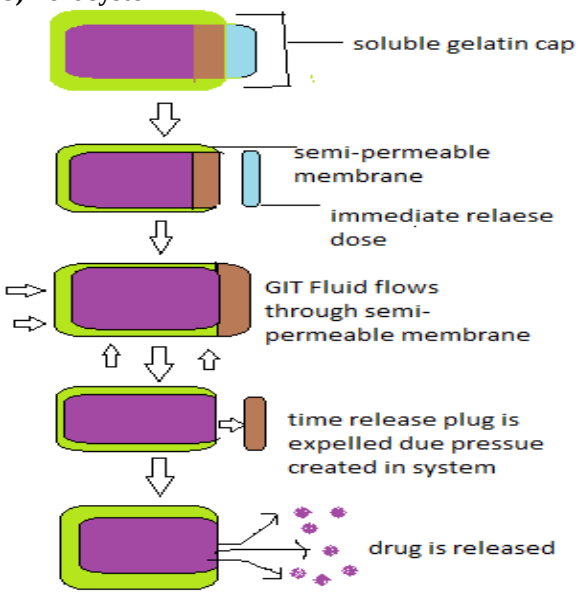
8) Pulsatile colon targeted drug delivery system

a) Pulsincap system.[14]



In this system the formulation is developed in capsule form, hydrogel plug is used which seals the drug content.Pulsincap system is made up of soluble gelatin cap and swellable hydrogel plug in capsule body.First the soluble gelatin cap dissolves; the dissolution fluid comes in contact with swellable hydrogel plug, the plug swells and after a lag time gets pushed off to release the drug contents.Polymers used as hydrogel plugs – HPMC of different grade, polyvinyl acetate, polymethyl methacrylate.The lag time is controlled by length & Point of interaction in capsule body.

b) Port system[19,20]



The system consists of capsule body surrounded by semi-permeable membrane.Capsule body consist of insoluble plug containing osmotically active agent & drug formulation.Soluble gelatin capsule dissolves first.When capsule body comes in contact with dissolution fluid the semi-permeable membrane permit the flow of dissolution fluid in the capsule leading to development of pressure in the capsule leading to expelling of plug & release of drug.The drug is released at regular interval with time gap between the successive intervals.

CONCLUSION

Colon targeted oral drug delivery system has gained increasing interest by formulation scientists.Colon targeted drug delivery system help in treatment of colonic as well as non – colonic diseases.Colon specific drug delivery provides safety, efficacy, and patient compliance.The hurdles in colon targeted drug delivery e.g. wide range of pH were overcomed by formulation approaches.The colon enzymes have adequate metabolizing capacity and aid in colon targeted drug delivery.Biodegradable polymers can be used for successful colon specific delivery of drug.The newer approaches are more specific compared to primary approaches.To ensure efficacy, targeted specificity, patient compliance, there is need of combination of conventional & new approaches.

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