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NOVEL DRUG DELIVERY APPROACHES FOR COLONIC DRUG DELIVERY SYSTEM: A REVIEW

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Abstract:

Colon related diseases is the world-wide health problem in which Colorectal cancer is the second most dangerous type of cancer, affecting both men and women. The modern diet and lifestyles, with high meat consumption and excessive alcohol use, along with limited physical activity has led to an increasing mortality rate for colon cancer worldwide. As a result, there is a need to develop novel drug therapies for colon related diseases. Colon specific drug delivery system (CDDS) has attracted significant attention during the past 20 years in providing several therapeutic advantages particularly for drugs that are sensitive to acidic condition and to intestinal enzymes. The colon is a site where both local and systemic delivery of drug can takes place. Oral drug delivery to treat colonic diseases encounters many problems like drug stability in the harsh environment of upper GI tract. Sustained colonic release of drugs can be useful in the treatment of nocturnal asthma, angina and arthritis while site specific release strategy is needed for local action for condition involving colonic pathologies such as ulcerative colitis, colorectal cancer and crohn's diseases. This review is focused on primary and novel drug delivery formulation and approaches for colonic drug delivery through pH sensitive system, microbially triggered system, time release system, osmotically controlled drug system, pressure dependent release system, probiotic approach, chronotropic system, Pulsincap system, prodrug approach, Enterion capsule based system, port system, CODES™ approach, COLAL-PRED approach, multiparticulate based system.
Keywords: CDDS, Ulcerative colitis, colorectal cancer, CODES™.

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INTRODUCTION:

Various drug delivery approaches have been utilized for successful delivery of drugs to the target site. However, the oral route of administration is considered to be the most convenient and preferred route for a sustained as well as controlled drug delivery system [1]. Where drugs normally dissolves in the gastro-intestinal (GI) fluids and is absorbed from these regions of gastro-intestinal tract (GIT), and both process depend upon physiochemical properties of drug [2]. Targeting of drug specifically to the colon is advantageous in the treatment of various diseases such as amoebiasis, Crohn's disease, ulcerative colitis and colorectal cancer. In addition, it has shown great potential in the oral delivery of therapeutic peptides and proteins which are unstable in the upper part of gastro-intestinal tract (GIT) [3]. Apart from protecting these labile molecules, colon also offers an opportunistic site for oral delivery of vaccines because it is rich in lymphoid tissue. A colonic targeted approach found to be effected in minimizing uncertain side effects. So the colon as a site for drug delivery, offers distinct advantages on account of near neutral pH, a much longer transit time, relatively low proteolytic activity and offers a much greater responsiveness to absorption enhances [4]. This delivery system can be also used in certain conditions where drugs should be delivered after a lag time, like in Chronopharmacotherapy of diseases showing circadian rhythms in their pathophysiology [5]. Rectal route of drug administration is also found to be shortest route for targeting drug to colon. Although approaching the proximal part of colon is not easy via rectal route of administration. Rectal administration of drug offers less compliance and is also uncomfortable for patients [6]. Overall, there is less free fluid in the colon than in the small intestine and hence, dissolution could be problematic for poorly water-soluble drugs. In such instances, the drug may need to be delivered in a presolubilized form, or delivery should be directly to the proximal colon, as a fluid gradient exists in the colon with more free water present in the proximal colon 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 free concentration of drug. Moreover, the resident micro-flora could also affect colonic performance via degradation of the drug [7]. Micro-encapsulation is now the most frequently employed method of producing controlled release dosage forms. Microcapsules developed for used in medicine consisting of solid or liquid core material containing one or more drugs enclosed in coating [8]. Target sites, colonic disease conditions, and drugs used for treatment are shown in table [9].

Advantages of colon target drug delivery system [6, 10, 11]:

1. It is suitable for drug degraded by the enzymes in stomach and small intestine.
2. The wastage of drug by unnecessary systemic absorption is reduced and intact from of the drug is saving till reaches target site.
3. Predictable, reproducible and short gastric residence time.
4. Less inter and intra-subject variability.
5. Improve bioavailability.
6. Limited risk of local irritation.
7. No risk of dose dumping.
8. Improve stability.
9. Improve patient comfort and compliance.
10. Achieve a unique release pattern.
11. Reduced gastric irritation caused by many drugs (e.g. NSAIDS)
12. Extended day time or night time activity.
13. Minimize first pass metabolism.
14. For the treatment of nicotine addiction.
15. Diseases sensitive to circadian rhythms such as asthma, angina and arthritis are treated efficiently by colon targeting of drugs.
16. Decreased frequency of administration. Hence decreased cost of drugs.

Limitations of colonic drug delivery [2, 12]:

The development of a colon-specific drug delivery system is associated with specific limitations and challenges.

- Difficult to access colon.
- The GIT physiology is complex and has a wide range of pH values, fluid volumes, and transit times.
- The non-specific interactions of drug with the colonic content e.g., dietary residues, intestinal secretions, mucus, or faecal matter.
- Successful delivery requires the drug to be in solution before it arrives in the colon, but the fluid content in the colon is lower and more viscous than in upper GIT, which is the limiting factors for poorly soluble drugs.
- Lower surface area and relative tightness of the tight junction in the colon can restrict drug transport across the mucosa into the systemic circulation.

Table 1: Target Sites, Colonic Disease Conditions, and Drug Used For Treatment:

Target sites	Disease condition	Drug and active agents
Topical action	Inflammatory bowel diseases, Irritable bowel diseases, Crohn's diseases, Chronic pancreatitis	Hydrocortisone Budesonide Prednisolone Sulfasalazine Olsalazine
Local action	Pancreatectomy and Cystic fibrosis, Colorectal cancer	Digestive enzyme supplements, 5-Flurouracil
Systemic action	To prevent gastric irritation To prevent first pass metabolism of orally ingested drugs Oral delivery of peptides Oral delivery of vaccines	NSAIDS Steroids Insulins

Anatomy of large intestine [2]:

The large intestine, which is about 1.5 m long and 6.5 cm in diameter, extends from the ileum to the anus. It is attached to the posterior abdominal wall by its mesocolon. Structurally, four major regions of the large intestine are the cecum, colon, rectum and anal canal. The opening from the ileum into the large intestine is guarded by ileocecal sphincter, which allows passing of materials from small intestine into the large intestine. Hanging inferior to the ileocecal valve is the cecum, a small pouch about 6 cm long. The open end of the cecum attach with a long tube called the colon, which is divided into ascending, transverse, descending, and sigmoid portions. The ascending colon ascends on the right side of the abdomen, reaches the inferior surface of liver and continues across the abdomen to the left side as transverse colon. It curves beneath the inferior end of the spleen on the left side and passes inferiorly towards iliac crest as the descending colon. The sigmoid colon begins near the left iliac crest and terminates as the rectum. Rectum is 20 cm long last portion of the GI tract, lies anterior to the sacrum and coccyx.
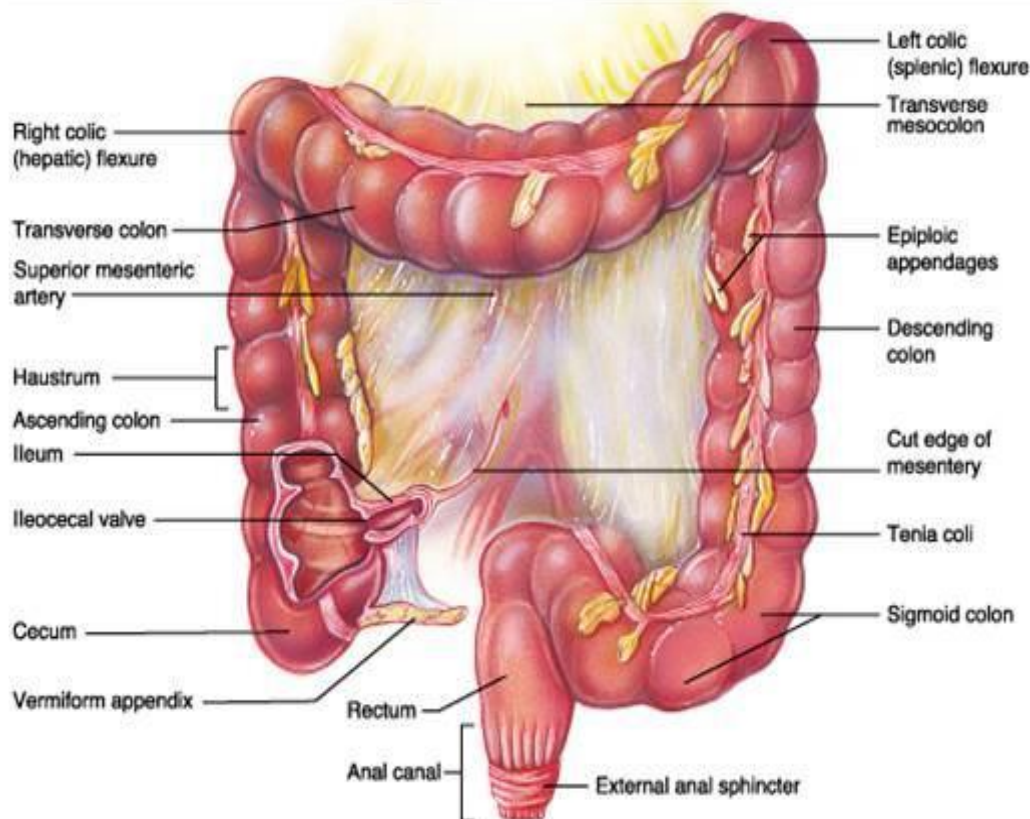
Fig. 1: Anatomy of Colon

Physiology of large intestine [2]:

Large intestine promote the growth of various microorganism by offering friendly environment which play a key role in digestion of proteins, carbohydrates into their simpler form by secreting various enzyme. Large intestine help in maintaining optimum body water balance through the absorption of water about 100-200 mL via osmosis, also absorb ions like sodium, chloride and vitamins like B and K.

Rationales for colon targeting [13]:

The rationales for development of orally administered colonic drug delivery system include:

I.   The opportunity to reduce adverse effects in the treatment of local colonic disorders.

II. Elucidation of the mode of action of some non-steroidal anti-inflammatory drugs (NSAIDs) such as sulindac.

III. The recognition that the colon is capable of absorbing drug efficiently.

IV. Accumulated evidence that drug absorption enhancement works better in the colon then in the small intestine.

V.   The anticipation that protein drugs can be absorbed better from the large bowel owing to the reduced proteolytic activity in this organ.

VI. The unique metabolic activity of the colon that makes it an attractive organ for the design of drug delivery system.

Factors affecting colon targeted drug delivery [14]:

1. Physiological factors
2. Pharmaceutical factors

1. Physiological factors

a. Gastric emptying

Drug delivery 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 upon 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 transits times.

Table: 2 Transit Time of Different Parts of Git [14]:

Part of GIT	Transit time
Fasted state	10 min– 2 hr
Fed state	> 2 hr
Small intestine transit	3 – 4 hr
Colon transit	20 – 35 hr

b. pH of colon

The pH of GIT varies between different individuals. The food intakes, diseased state, etc. Influences the pH of 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 to the site.

c. Colonic microflora and enzymes

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

Table: 3 pH In Different Parts of Colon [14]:

Part of GIT	pH
Stomach	Fasted state 1.5-2 Fed state 2-6
Small intestine	6.6-7.5
Colon Ascending colon Transverse colon Descending colon	 6.4 6.6 7.0

Table: 4 Different Microflora, Enzymes Released and Action [14]:

Microorganism	Enzymes	Metabolic reaction
E.coli, Bacteroids	Nitroreductase	Reduces aromatic & heterocyclic nitro compounds
Clostridia, Lactobacilli	Hydrogenase	Reduces carbonyl group & aliphatic double bonds
Clostridia, Eubacteria	Glucosidase	Cleavage of glycosidase of alcohols & phenols
Eubacteria, Clostridia, Streptococci	Sulfatase	Cleavage of Osulphates & Sulfamates

Table: 5 Criteria for Selection of Drugs for CDDS

Criteria	Pharmacological class	Non-peptide drugs	Peptide drugs
Drugs used for local effect 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 drugs	Pseudoephedrine	Epoetin, Glucagon
Drugs that are degrade in stomach and small intestine	Peptides and Protein	Bromophenaramine, 5-Fluorouracil, Doxorubicin	Gonadoreline, Insulin, Interferons
Drugs that undergo extensive first pass metabolism	Nitroglycerin and Corticosteroids	Bleomycin, Nicotine	Protirelin, Sermorelin, Saloatonin
Drugs for targeting	Antiarthritic and Antiasthamatic drugs	Prednisolone, Hydrocortisone, 5-Aminosalicyclic acid	Somatropin, Urotoilitin

2. Pharmaceutical factors

a. Drug carrier

The selection of carrier for CDDS depends on the nature of 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 group of drug molecule etc.

Criteria for selection of drugs for colon-specific drug delivery system [9, 15, 16]:

The best candidates for CDDS are drugs which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of IBD, ulcerative colitis, diarrhoea, and colon cancer are ideal candidates for colon delivery. Drugs for colon cancer that are degrade in stomach and small intestine. Drugs that undergo extensive first pass metabolism. Drugs poorly absorbed from upper GIT. Drugs for targeting. The criteria for selection of drugs for CDDS are summarized in table:

General consideration for design of colonic formulations [9, 17]:

Formulations for colonic delivery are, in general, delayed released dosage forms which may be designed either to provide a burst release or a sustained/prolonged/targeted release. The delivery system design is decided based on;

a. Pathology of disease, especially the affected parts of the lower GIT.

b. Physicochemical and biopharmaceutical properties of the drug such as solubility, stability and permeability at the intended site of delivery.

c. The preferred site and release rate data of the drug: Very common physiological factor which is considered in the design of delayed release colonic formulations is pH gradient of the GI tract. In normal healthy subjects, there is a progressive increase in luminal pH from the duodenum (pH is 6.6 ± 0.5) to the end of the ileum (pH is 7.5 ± 0.4), a decrease in the cecum (pH is 6.4 ± 0.4) and then a Slow rise from the right to the left colon with a final value of 7.0 ± 0.7.

Formulation of drugs for colonic delivery also requires careful consideration of drug dissolution and/or release rate in the colonic fluids. The poor dissolution and release rate may in turn led to lower systemic availability of drugs. These issues could be more problematic when the drug candidates is poorly water soluble and requires high doses for therapy.

DRUG ABSORPTION IN COLON [18, 19, 20]:

Drugs are absorbed passively by either paracellular or transcellular route. Transcellular absorption involves the passage of drugs through cells and this is the route most lipophilic drugs takes. Paracellular absorption involves the transport of drug through the tight junction between the cells and is the route most hydrophilic drugs takes. The slow rate if transit in colon lets the drug stay in contact with the mucosa for a longer period than in small intestine which compensates the much lower surface area. The colonic contents become more viscous with progressive absorption of water as one travels further through the colon. This causes a reduced dissolution rate, slow diffusion of dissolved drug through the mucosa. Theoretically, drug absorption can occur along the entire GI tract, while in actuality, most drugs are absorbed in the duodenum and proximal jejunum.

- **Drugs which is well absorbed**
  Glibenclamide, Diclofenac, Theophylline, Ibuprofen, Metoprolol and Oxyprenolol.
- **Drugs which poorly absorbed**
  Furosemide, Pyretanide, Buflomedil, Atenolol

POLYMERS USED IN COLON TARGETING [21]:

Polymers are becoming increasingly important in the field of drug delivery. Advances in polymer science have led to the development of several novel drug delivery systems. These newer technological development include drug modification by chemical

means, career based drug delivery and drug entrapment in the polymeric matrices or within pumps that are placed in desired bodily compartments.

BIODEGRADABLE POLYMERS [21]:

Biodegradable polymers have been widely used in biomedical applications because of their known biocompatibility and biodegradability. Polymers within this group retain their properties for a limited period of time and then gradually degrade in soluble molecules that can be excreted from the body. However, biodegradable materials do produce degradation by-products that must be tolerated with little or no adverse reactions within the biological environment.

Table: 6 List of Biodegradable Polymers Used in Drug Delivery [21]:

Natural polymers	Synthetic polymers
Pectin	Eudragit L 100
Chitosan	Eudragit S 100
Guar gum	Eudragit L 30D
Dextran	Eudragit RS 30D
Cyclodextrin	Eudragit L100-55
Inulin	Polyvinyl acetate phthalate
Xanthan gum	Hydroxyl propyl ethyl cellulose
Amylose	phthalate 50
Locust bean gum	Hydroxyl propyl ethyl cellulose phthalate 55
Alginates	Cellulose acetate trimelliate
Chondroitin sulphates	Cellulose acetate phthalate
Shellac	

Natural polymers in colon targeting [21]:

Natural polysaccharides are extensively used for the development of solid oral dosage form for colonic delivery of drugs. These polymers are generally hydrophilic in nature and have limited swelling characteristics in acidic pH. Various bacteria present in the colon secrets many enzymes which can cause hydrolytic cleavage of glycosidic bonds e.g. β-D-galactosidase, amylase, pectinase, β-D-glucosidase, dextranase etc. These polymers are inexpensive and are available in variety of structures. Pectin, starch, guar gum, amylose, are a few polysaccharides commonly used in dosage forms.

Pectin [17, 22]:

Pectin are non-starch, linear polysaccharides extracted from the plant cell walls. It contains backbone of α-1, 4 d-galacturonic acid and 1, 2 L-rhamnose with D-galactose and L-arabinose side chains. It is degraded by colonic bacterial enzymes but remains intact in stomach and small intestine. Due to its water solubility, pectin needs structural modifications for its utility in targeted delivery. Matrix tablets of calcium pectinate showed promising results *in vitro*. Pectin alone is unable to protect the load of drug as GI fluids penetrates into and releases the drug by diffusion. This problem can

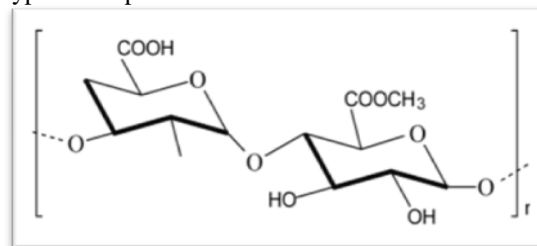be manipulated through choice of suitable pectin type or the presence of additives.

Fig. 2: Chemical structure of Pectin

Guar gum [17]:

Guar gum, also called guaran, is a galactomannan polysaccharide (β-1, 4 D-mannose, α- 1, 6 D-galactose). It has low hydrophilicity but hydrates and swells in cold water forming viscous dispersion or sols. It is liable to galacto-mannose enzyme in the large intestine. Guar gum based pellet system were prepared by coating guar gum and pH-sensitive polymer Eudragit FS 30D successively around drug loaded non-pareil cores.
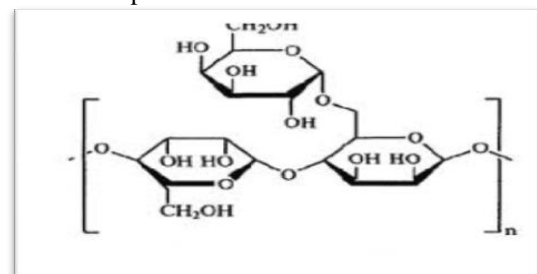

Fig. 3: Chemical structure of guar gum

Chondroitin sulphate [17]:

Chondroitin sulphate is a soluble muco-polysaccharide comprising of β-1, 3 D-glucuronic acid linked to N-acetyl-D-galactosamine. It is the substrate for the bacteroides species in the large intestine. Natural chondroitin is freely water soluble and may not be able to sustain the release of many drugs from the matrix.
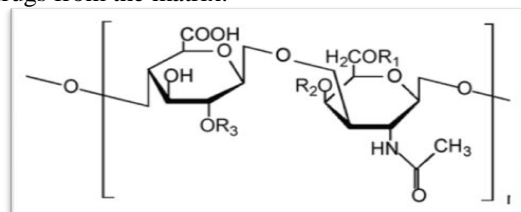

Fig. 4: Chemical structure of chondroitin sulphate

Chitosan [17]:

Chitosan is derived from the chitin, a fibre like substance. Chitin and chitosan both have similar chemical structures. Chitosan is consisting of the repeated units of (2-amino-2-deoxy-D-gluco-pyranose) which are linked by (1, 4) β-bonds. Chitosan is nontoxic, biodegradable, biocompatible and bioactive polymer. [28Chitosan-polyanions complexes have been widely investigated for the application like drug and protein delivery, cell transplantation, enzyme immobilization, among these complexes, chitosan-alginate complex may be the most important drug delivery hydrogel system.
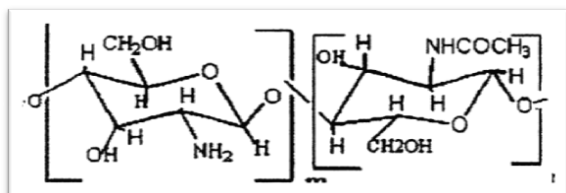
**Fig. 5: Chemical structure of Chitosan**

Alginates [23]:
Alginates is non-toxic, biodegradable, naturally occurring polysaccharide obtained from marine brown algae, certain species of bacteria. Sodium alginate is sodium salt of alginic acid a natural polysaccharide. Sodium alginate is soluble in water and form a reticulated structure which can be cross-linked with divalent and polyvalent cations to form insoluble meshwork. Calcium and zinc cations have been reported for cross-linking of acid group of alginate. Its unique property of forming water insoluble calcium alginate gel through ionotropic gelation with calcium ions is simple, mild and eco-friendly condition has made possible to encapsulate macromolecular bio-active agents like cell, enzyme, protein and vaccine.
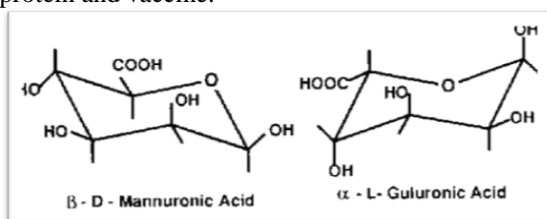
Fig. 6: Chemical structure of Alginate

Dextran [24]:
Dextran, a carbohydrate is used to prepare hydrogel type of biodegradable and biocompatible systems. It can be chemically modified that provide higher percentage of drug or protein incorporation. The rate of degradation of dextran microspheres depends entirely on the degree of substitution of dextran and the amount of dextranase enzyme incorporated. The major advantage of dextran water in water emulsion technique is that no organic solvent is used, which might have adverse effect on the stability of drug or protein and second, protein is largely allowed to release through the water filled pores.
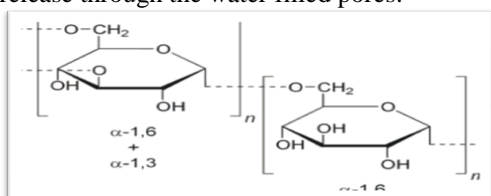

Fig. 7: Chemical structure of Dextran

Amylose [17]:
It is poly (1-4-α-D-glucopyranose) that consists of D-glucopyranose residues linked by α- (1-4) bonds. Those substances, present naturally in diet, have the advantages of being safe, non-toxic and easily available. These are resistant to pancreatic α-amylase, but are degraded by colonic bacterial enzyme. Mixed film of amylose and ethyl cellulose

as coating has shown a great potential as colon delivery carriers. Delayed release composition comprising glassy amylose and an active compound were designed to permit the release when the composition reaches the large intestine. This composition is useful in the diagnosis and therapy of diseases of the colon.
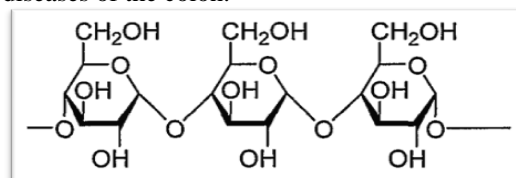
Fig. 8: Chemical structure of Amylose

Inulin [25, 26]:
Inulin is a naturally occurring polysaccharide found in many plants. It consists of β-2, 1 linked D-fructose molecules having a glucosyl unit at the reducing end. It is not hydrolysed by the endogenous secretions of human digestive tract. It is metabolized in the colon. Inulin HP (high degree polymerization) was incorporated in Eudragit RS film was evaluated as a possible biodegradable coating for colonic drug delivery. In addition to this inulin shows a prebiotic effect as it is fermented in anaerobic conditions of colon and results in proliferation of Bifidobacterium in the lower colon. Owing to these properties inulin has found a variety of applications in the food industry such as fat replacement, fibre supplement, prebiotic and bulk enhancer. Inulin, being a natural and bio-safe polymer with selective digestion in lower colon, was hence selected as a suitable candidate for the development of a colon targeted drug delivery system.
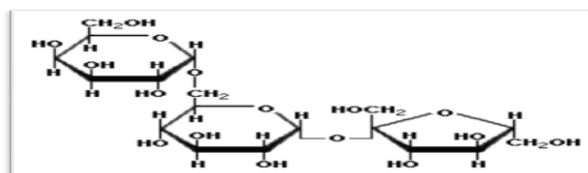
Fig 9: Chemical structure of Inulin

Locust bean gum [27]:
It is derived from carob (Ceratonia siliqua) seeds. This is neutral polymer slightly soluble in cold water. From in vitro and in vivo studies revealed that locust bean and chitosan was capable of protecting the drug from being release in the stomach and small intestine and was susceptible to colonic bacterial enzymatic actions with resultant drug release in the colon.
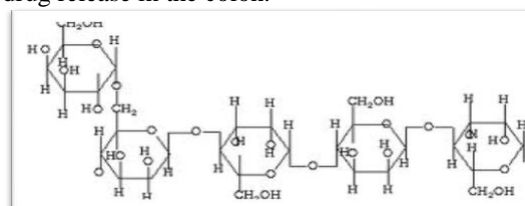
Fig 10: Chemical structure of Locust bean gum
Approaches used for Site specific drug delivery to colon (CDDS) [28]:

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

Primary approaches for CDDS:

Prodrug approach [29]:

A prodrug is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in vivo to release the active drug. It should have improved delivery properties over the parent drug molecule. Various types of prodrugs with drug molecules linked to different carriers have been prepared and evaluated for colon-specific delivery agents. The parameters evaluated include absorption and stability of prodrug in upper GIT (hydrolysis in various GIT segments, both in GIT contents and GIT tissues), selectively of hydrolysis by the enzymes of the colon, and the amount of drug regenerated in the colon. Amino-acid, glycoside, glucuronide and azo conjugates are some of the conjugates evaluated for colon-specific delivery.

Amino-acid conjugates:

Protein and their basic units have polar groups like $-NH_2-$ and $-COOH-$. These polar groups are hydrophilic and reduce the membrane permeability of amino acid and proteins. Amino acid conjugates gave good results as a colon-specific carrier for salicylic acid. It showed minimal absorption and degradation in the upper GIT and showed more enzymatic specificity for hydrolysis by colonic enzymes. Also the drug showed maximum and sustained absorption from colon.

Glycoside conjugates:

Certain drugs can be conjugated to different sugar moieties to form glycosides. The glycoside may be glucoside, galactoside, or cellobioside depending upon whether the sugar moiety is a glucose, galactose or cellulose respectively. Because they are bulky and hydrophilic, these glycoside do not penetrate the biological membranes upon ingestion. They breakdown upon action of glycosidases, releasing the drug part from the sugar. The presence of Glycosidases activity in the small intestine could pose a problem in the delivery of these conjugates to the large bowel, because some hydrolysis of the conjugate can be expected in the small intestine. However the small intestinal transit time, is short, and moreover, considering the time required for the hydrolysis of glycosidic bond, these conjugates can be expected to be good colon specific drug carriers.

Glucuronide and sulphate conjugates:

Glucuronide and sulphate conjugation are the major mechanism for the inactivation and preparation for clearance of variety of drugs. Bacteria of the lower GIT, however, secrete β-glucuronidase and can deglucuronidate a variety of drugs in the intestine. Thus, the deglucuronidation process results in the release of active drug again and enables its reabsorption. Considering this, glucuronide prodrugs can be expected to be superior agents for drug delivery to the colon.

Azo conjugates:

The azo linkage exhibit a wide range of thermal, chemical, photochemical, and pharmaceutical properties. These azo compounds are extensively metabolized by the intestinal bacteria. The use of these azo compound for colon targeting has been in the form of hydrogels as a coating material for coating the drug cores and as prodrugs. In the latter approach the drug is attached via an azo bond to a carrier. This azo bond is stable in the upper GIT and is cleaved in the colon by the azo-reductase produced by the microflora.
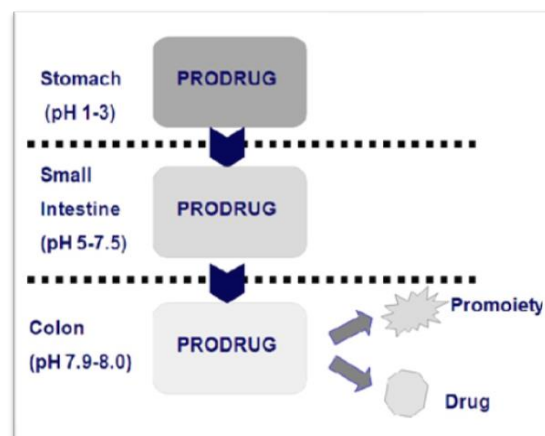

Fig. 11: Prodrug based colonic drug delivery

a) **pH sensitive polymer coated drug delivery to the colon [28, 30]:**

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 decline 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.

Polymers	Optimum pH for Dissolution
Eudragit L 100	6.0
Eudragit S 100	7.0
Eudragit L 30 D	5.6
Eudragit FS 30 D	6.8
Eudragit L 100- 55	5.5
Poly vinyl acetate phthalate	5.0
Hydroxy Propyl methyle cellulose phthalate	4.8
Hydroxy propyl methyle cellulose phthalate 50	5.2
Hydroxy propyl methyle cellulose phthalate 55	5.4
Cellulose acetate trimelliate	4.8
Cellulose acetate phthalate	5.0
Shllac	7.0

Fig. 12: Threshold pH of commonly used polymer for colonic delivery

The coating of pH-sensitive polymers to the tablets, capsules or pellets provide delayed release and protect the active drug from gastric fluid. The polymers used for colon targeting, however, should be able to withstand the lower pH values of the

stomach and of the proximal part of small intestine and also be able to disintegrate at the neutral or slightly alkaline pH of terminal ileum and preferably at the ileocecal junction. The problem with this approach is that the intestinal pH may not be stable because it is affected by diet, diseases and presence of fatty acids, carbon dioxide and other fermentation products. Moreover there is considerable difference in inter- and intra-individual gastrointestinal tract pH, and this cause a major problem in reproducible drug delivery to the large intestine.
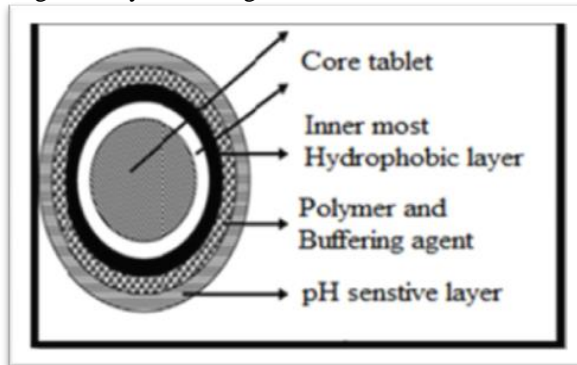
Fig. 13: pH sensitive polymer coated drug delivery

Microbial triggered drug delivery system [16, 31]:

Colon is rich in microflora and variety of microbes were found in colon, that obtained there basic requirement or fulfil their energy needs from the undigested foods present in small intestine such as di- trisaccharides via fermentation process. Bacterial count in colon is much higher around 1011-1012 CFU/ml with some 400 different species which are:

A. Fundamentally aerobic, predominant species such as bacteroides, Bifidobacterium, and eubacterium etc., whose major metabolic process occurring in colon are hydrolysis and reduction. The enzyme present in the colon are:

B. Reducing enzymes: Nitroreductase, Azoreductase, N-oxide reductase, sulfoxide reductase, hydrogenase etc.

**b. Delayed (Time Controlled Release) Release Drug Delivery to the Colon [25]:**

It also known as pulsatile release, delayed or sigmoidal release system. This approaches is based on the principle of delaying the release of the drug until it enters into the colon. Although gastric emptying tends to be highly variable, small intestinal transit time is relatively constant or little bit variation can be observed. The strategy in designing timed-released systems is to resist the acidic environment of stomach and to undergo a lag time of predetermined span of time, after which release of drug takes place. The lag time in this case is the time requires to transit from the mouth to colon. But due to enteric coating in most of these systems, the large variation in gastric emptying is overcome.

The main drawbacks of this delivery system were:

   i. Transit time varies in subject suffering from irritable bowel syndrome and ulcerative colitis

   ii. Peristaltic movement varies from person to person, and this makes difficult to predict colonic delivery time and leads to poor colonic availability of drugs.

**Enteric-coated time-release press coated tablets [32]:**

ETP tablets are composed of three components, a drug containing core tablet (rapid release function), the press coated swellable hydrophobic polymer layer and an enteric coating layer (acid resistance function). Tablet does not release drug in stomach due to resistance of outer enteric coating layer. After gastric emptying, the enteric coating layer rapidly dissolves and intestinal fluid begins slowly erode the press coated polymer (HPC) layer and when erosion front reaches the core tablet, rapid drug release occurs since the erosion process takes a long time there is no drug release period (lag phase) after gastric emptying. The duration of lag phase controlled either by weight or composition of polymer (HPC) layer.
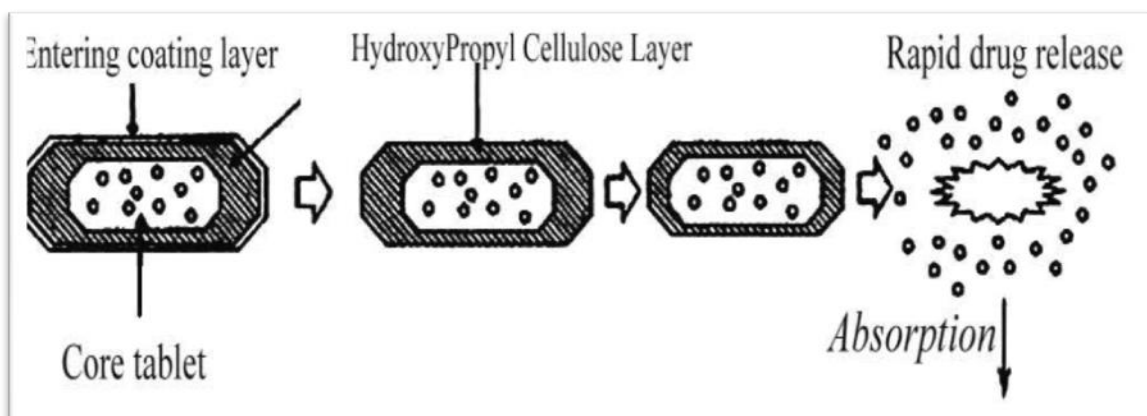
Fig. 14: ETP Tablet

Novel approaches for colon targeting:
Osmotic controlled drug delivery (OROS-CT) [33]:
The OROS-CT (Alza Corporation) can be used to target the drug locally to the colon for the treatment of diseases 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 4mm in diameter, encapsulated within a hard gelatin capsule. Each push pull units contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. An orifice is drilled into the semipermeable membrane to the drug layer. The outside surface of semipermeable membrane is coated with Eudragit S 100to delay the drug release from the device during its transit through the stomach. Upon arrival on the small intestine the coating dissolves at pH≤7. As a results water enters the unit causing the osmotic push compartment to swell forcing the drug out of the orifice into colon.
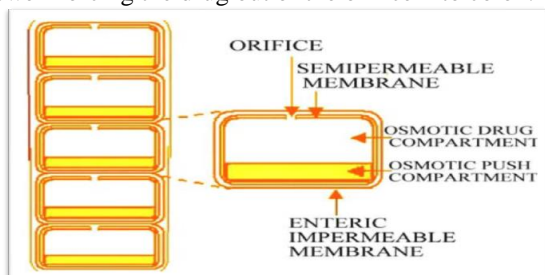

Fig. 15: OROS-CT

Pressure controlled drug delivery system [34, 38]:
As a result of peristalsis, higher pressure 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 colon. The thickness of ethyl cellulose membrane is the most important factor for disintegration. 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. Lag time of three to five

hours in relation to drug absorption were noted when pressure-controlled capsules were administered to human.

Pulsatile drug delivery system:
Pulsincap system [17]:
A drug delivery system, from which there is rapid drug release after a specific lag time, was developed to allow release of drug in the large intestine. This system consists of water insoluble capsule enclosing the drug reservoir. A swellable hydrogel plug was used to seal drug content into capsule body to prepare a single unit formulation. The plug, which gets pushed away by swelling or erosion and the drug is released as a pulse from the insoluble capsule body. Polymers used for hydrogel plug were of 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.
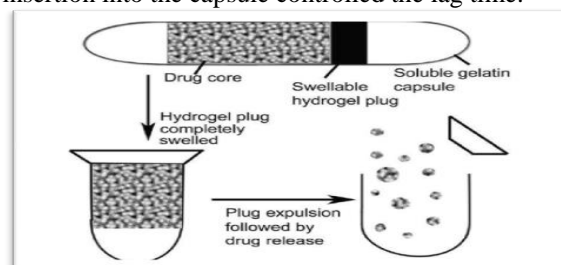
16: Pulsincap system

Port system [35]:
The port system 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. When this capsule comes in contact with the dissolution fluid, the semi permeable membrane allows the entry of water leading to the pressure development inside the capsule and the insoluble plug expelled after a lag time. The dosage form is designed in such a manner that after ingestion, the first drug release pulse occur within 1-2 hr, followed by period during which no release occur, second dose is release in 3-5 hr of ingestion. This is again followed by a second no release interval. Release of third dose occurs within 7-9 hr of ingestion. This system avoids the second time of dosing.


Fig. 17: Port system

Probiotic approaches [36]:
The probiotic approaches is one of the latest approaches for colon targeting. In this approach, three components are desirable namely probiotic strain, microbially digestable carrier and triggering temperature. Probiotic strains include inactive microflora 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 gained success in colon drug delivery system because these conditions are only available in colon.

Chronotropic system [36]:
In this technology, the drug release after a particular lag time, surrounding with a soluble barrier layer, which consist of a core containing drug reservoir coated by a hydrophilic polymer like HPMC. The coating of additional enteric coating film outside that layer to overcome the gastric emptying variability and lag time of the drug was controlled by coating thickness and viscosity grade of polymer.
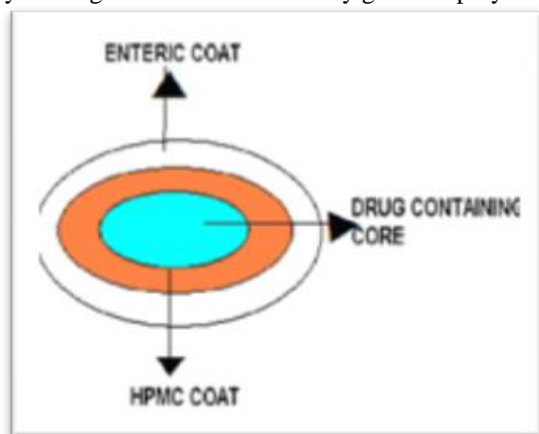

Fig. 18: Chronotropic system

COLAL-PRED SYSTEM [2, 36]:
COLAL-PRED is a proprietary gastrointestinal product developed by Alizyme for the treatment of ulcerative colitis. It is an effective anti-inflammatory treatment for ulcerative colitis without the typical side effects of steroids. There is no competitor of this product yet in the market. COLAL-PRED has a coating which is break only in colon use in topical deliver of prednisolone in ulcerative colitis. Its colon targeting is done by coating it with such substances which get degraded by the colonic bacteria.

CODES™ [32]:
CODES™ is a unique CDDS technology that was design to avoid the inherent problems associated with pH or time dependent system. CODES™ is combined approach of pH dependent and microbially triggered CDDS. It has been developed by utilizing a unique mechanism involving lactulose, which acts as a trigger form site specific drug release in the colon. The system consists of traditional tablet core containing lactulose, which is over coated with an acid soluble material, Eudragit E, and then subsequently over coated with an enteric

material, Eudragit L. the acid soluble material coating then protects the preparation as it passage through the alkaline pH of small intestine. Once the tablet arrives in the colon the bacteria will enzymatically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH of surrounding to affect the dissolution of acid soluble coating and subsequent drug release.
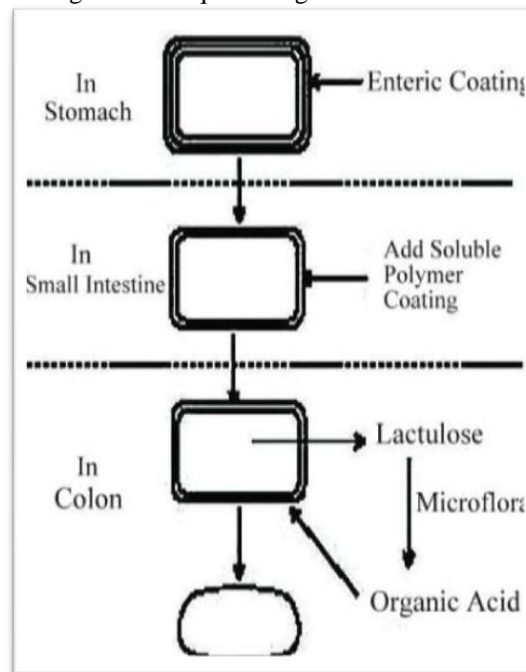
Fig. 19: CODES™

Multiparticulate system for colon targeting [15, 17, 39]:
Multiparticulate approaches include formulations in the form of pellets, granules, beads, microparticles and nanoparticles. Because of their smaller particle size as compare to single unit dosage forms these system are capable of passing through the GI tract easily, leading to less inter and intra-subject variability. Moreover multiparticulate systems tends to be more uniformly dispersed in the GI tract and also ensure more uniform drug absorption.

Microspheres based colon targeted system:
It was well documented that microspheres made up of biodegradable polymers could be taken up by macrophages. Hence the use of microspheres for site-specific delivery of anti-inflammatory agents could be utilized as a potential tool for effective management of IBD. The systemic absorption of peptide drugs through the colon has great attention due to low proteolytic enzyme activity and hence several insulin delivery system based on microspheres have been reported in literature.

Nanoparticulate based system:
A nanoparticle helps in cell specific targeting by attaching drug molecules to the designed carriers. Nano sized colloidal drug delivery systems developed by polymers (natural or synthetic) have also been evaluated for colon specific drug delivery. Various orally administered drugs showed enhanced

solubility, permeability and bioavailability through nanoparticles to the colon. Various polymeric nanoparticles were examined by drug delivery researchers for the delivery of protein and various peptide drugs. The use of nanoparticles for bioadhesion purposes has also been investigated. Nanoparticles have large specific surfaces which is indicative of high interactive potential with biological surfaces. Since the interaction is of nonspecific nature, bioadhesion can be induced by binding nanoparticles with biological surfaces.

Enterion capsule technology [40]:
The Enterion capsule has recently been developed by Phacton Research, Nottingham, UK, for targeted delivery of a wide range of different drug formulations into any region of the gut. It is a 32-mm long, round-ended capsule and contains a drug reservoir with a volume capacity of approximately 1 ml. with either a liquid formulation (e.g. Solution, suspension) or a particulate formulation (e.g. Powder, pellets) through an opening 9 mm in diameter, which is then sealed by inserting a push-on cap fitted with a silicone O-ring. The floor of the drug reservoir is the piston face, which is held back against a compressed spring by a high tensile strength polymer filament.

Table: 7 Marketed Drug Products for the Treatment of Various Disease of Colon [41]:

S. No	MARKETED NAME	COMPANY NAME	DISEASE	DRUG
1	Mesacol Tablet	Sun Pharma, India	Ulcerative colitis	Mesalamine
2	Mesacol Enema	Sun Pharma, India	Ulcerative colitis	Mesalamine
3	Asacol	Win-Medicare, India	Ulcerative colitis, crohn's disease	Mesalamine
4	SAZO	Wallace, India	Ulcerative colitis, crohn's disease	Sulphasalazine
5	Intazide	Intas, India	Ulcerative colitis	Balsalazide
6	Lomotil	RPG Life, India	Mild ulcerative colitis	Diphenoxylate HCl, atropine sulphate
7	BUSCOPAN	German Remedies, India	Colonic motility disorder	Hyoscine butyl bromide
8	COLOSPA	Solvay, India	Irritable colon syndrome	Mebeverine
9	CYCLOMINOL	Neol, India	Irritable colon syndrome	Diclomine
10	Eldicet	Solvay, India	Irritable colon syndrome, spastic colon	Pinaverium bromide
11	Equirex	Jagsonpal Pharmaceutical, India	Irritable colon syndrome	Clordiazepoxide
12	Normaxin	Systopic Labs, India	Irritable colon syndrome	Clidinium bromide
13	Pro-banthine	RPG Life, India	Irritable colon syndrome	Propenthiline bromide
14	Entofoam	Cipla, India	Ulcerative colitis	Hydrocortisone Acetate

CONCLUSION:

The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. The novel approaches are more specific compared to the primary approaches. The in vitro evaluation studies used by far doesn't provide the exact Invitro in vivo correlation due to several reasons. In future by combining various strategies, colon targeted drug delivery will find the central place in novel drug delivery.

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