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COLON: DISEASES AND APPROACHES- AN OVERVIEW

Surender Verma, Sapna Saini*, Mahima Kaul and Aruna Rawat
Institute of Pharmaceutical Sciences, Kurukshetra University
Kurukshetra-136119, Haryana, India.
Email: 01sapnalongia@gmail.com

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Abstract

Over decades, colon targeted drug delivery systems have been gaining significant attention not just for providing more effective therapy to colon related disease, but also as a potential approach for systemic delivery of therapeutic proteins and peptide drugs. A successful and precise colon drug delivery system requires a drug to be protected from upper gastrointestinal tract and an abrupt release into the optimum site of the colon i.e. proximal colon. Remarkable advances and progresses in colon specific drug delivery have been made. This review is an attempt to revise the basic concepts and aspects of colon targeted drug delivery systems and also encompasses an overview of diseases of the colon, namely, IBD, ulcerative colitis, crohn's disease and colon cancer. The various primary and novel approaches for effective targeting in the colon have also been discussed. The marketed products for different approaches are also listed.

Keywords: Colon, Gastrointestinal tract, colorectal cancer, Chronotherapy, Circadian rhythm

1. Introduction

Although oral delivery has become a widely accepted route of administration of therapeutic drugs, the gastro intestinal tract presents several formidable barriers to drug delivery.[1] It has serious drawback in conditions where localized delivery of the drug in the colon is required or in the condition where a drug needs to be protected from hostile environment of the upper region of the gastrointestinal tract.[2] Colon specific drug delivery system should

be capable of protecting the drug en route to the colon i.e. drug release and absorption should not occur in the stomach as well as in the small intestine, but the drug only released and absorbed once the system reaches to the colon.[3] Colonic delivery offers numerous therapeutic advantages like drugs, which are destroyed by the stomach acid and metabolized by pancreatic enzymes are minimally effected in the colon.[4] In addition to providing more effective therapy of the colon related diseases such as irritable bowel disease including ulcerative colitis and crohn's disease, amebiosis, colonic cancer and local colonic pathologies, colon-specific delivery has potential to address important unmet therapeutic needs including oral delivery of macromolecular drugs.[5] Colon is also a potential site for treatment of disease sensitive to circadian rhythms such as asthma, angina, arthritis, etc.[6] Various colon specific drug delivery systems are being developed by taking advantages of the luminal pH in the ileum and microbial enzymes in the colon.[7] In general, four primary approaches have been proposed for colon-specific delivery namely prodrugs, pH- dependent, time dependent, and microflora-activated systems.[8] Most recently new colon specific delivery system are developed .These are pressure controlled colon delivery capsule, CODESTM, osmotically controlled drug delivery system, pulsincap system, time clock system etc. [9]

Some diseases and drugs which are generally used for the colon targeting sites as shown in table 1.[10]

Table 1: Colon targeting sites, Diseases and Drugs.

Targeted sites	Diseases	Drugs
Topical action	Inflammatory bowel syndrome, Inflammatory bowel disease, Crohn's disease, Chronic pancreatic	Hydrocortisone, Budesonide, Prednisolone, Sulfasalazine
Local action	Pancreactomy, cystic fibrosis, colorectal cancer	Digestive enzyme supplements, 5-Flouro Uracil
Systemic action	To prevent gastric irritation and first pass metabolism	NSAIDS, Steroids

Rational for the development of oral colon targeted drug delivery [11]

Treatment of local pathologies

Chronotherapy (asthma, hypertension, cardiac arrhymias, arthritis or inflammation)

Greater responsiveness to the absorption enhancers

Less enzymatic activity

Site for delivery of delicate drugs (Proteins and Peptides)

Oral delivery of vaccines as it is rich in lymphoid tissue

2. Colonic diseases

Crohn's disease

Ulcerative colitis

Inflammatory bowel syndrome

Colon cancer

2.1 Inflammatory bowel diseases

Inflammatory bowel disease (IBD) is often localized to specific sites in the gastrointestinal tract (GIT) and comprised of two specific conditions:-

1. Ulcerative colitis (UC)
2. Crohn's disease (CD) [12]

Ulcerative colitis (UC) is an inflammatory destructive disease of the large intestine characterized by motility and secretion disorders such as acute flare-up, diarrhoea, bleeding ulcer, pus discharge etc. It may also be called as colitis or proctitis.[13, 14] It is thought to result from a dysregulated mucosal response in the intestinal wall facilitated by defects in the protective barrier function of the intestinal epithelium and the mucosal immune system.[15]

Crohn's disease (CD) differs from UC, because it causes deeper inflammation within the intestinal wall. There is discontinuous distribution of lesions and may involve any part of GIT from oral cavity to colon. It is an idiopathic, relapsing chronic inflammatory disease also called as regional enteritis. [13,16, 17]

2.2 Inflammatory bowel syndrome is characterized by a variable combination of unexplained chronic and recurrent symptoms attributed to intestine, abdominal pain, disturbed defecation (urgency, straining, incomplete evacuation, altered stool form and frequency) and bloatedness.[18]

2.3 Colorectal cancer results from an accumulation of mutation in tumor suppressor genes and oncogenes. Colorectal cancer is the second leading cause of cancer death in the United States and progresses through a series of clinical and histopathological stages ranging from single crypt lesions through small benign tumors (adenomatous polyps).[19]

3. Approaches used for site specific drug delivery to colon:

[A]- Primary approaches for CDDS

a) Microbially triggered drug delivery to colon.

i) Prodrug approach

ii) Polysaccharide based approach

b) pH sensitive systems

c) Delayed release or Time controlled release system

[B]- Newly developed approaches for CDDS

a) Pressure controlled drug delivery system (PCDDS)

b) CODESTM (a novel colon targeted delivery system)

c) Osmotic controlled drug delivery to colon (OROS-CT)

(A) Primary Approaches

(a) Microbial triggered colon targeted drug delivery system

The human colon is a dynamic and ecologically diverse environment containing over 400 distinct species of bacteria with a population of 10^{11} to 10^{12} CFU/ml with Bacteroides, Bifidobacterium, Eubacterium, Lactobacillus etc. greatly outnumbering other species (over 60% of total cultivable flora).[20] There are number of factors affecting the GIT microflora such as host factors including species, strain and individual differences, redox potential, bile salt, antibodies etc. age factor, GIT disorder, environmental factors such as diet, drug etc. and bacterial factors such as bacterial metabolites, pH etc.[21]

i) Prodrug approach

The specific delivery of drug to the colon by prodrug, polymeric prodrug and polymeric system has evoked a great interest in recent times.[22] Prodrug is pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in vivo to release the active drug. For colonic delivery of drugs, prodrugs are designed to minimal absorption and hydrolysis in the tracts of the upper GIT and undergo enzymatic hydrolysis in the colon, thereby releasing the active drug. [23]

Table 2: Prodrugs evaluated for colon-specific drug deliver with their in vitro/in vivo performance [24]

Carrier	Drug investigated	Linkage hydrolyzed	In vitro/ In vivo model used	Performance of the prodrug conjugate
Azo conjugates				
Sulphapyridine (SP)	5-ASA	Azo linkage	Human	Site specific with a lot of side effects associated with SP
p-Aminohippurate	5-ASA	Azo linkage	Human	The prodrug was site specific with lesser side effects
Amino acid conjugates				
Glutamic acid	Salicylic acid	Amide linkage	In vitro	Primary location of the hydrolysis of the prodrug was colon and the prodrug was not absorbed from the upper GIT
Saccharide carriers				
Glucose	Dexamethasone /prednisolone	Glycosidic linkage	Rat	Dexamethasone prodrug was site specific and 60% of oral dose reached the cecum . Only 15% of prednisolone prodrug reached the cecum
Glucuronide conjugates				
Glucuronic acid	Budesonide	Glucuronide linkage	Rat	Was found to be superior than budesonide itself for treatment of colitis
	Dexamethasone	Glucuronide linkage	Rat	A 30 fold increase in glucuronidase activity was found between distal small intestine and cecum of the normal rat

Dextan conjugates	Naproxen	Ester linkage	Rabbit	Drug regeneration took place in GIT. The relative bioavailabiliy of conjugates as compare to naproxen taken orally was 62%

ii) Polysacccharides Based Approach

The rationale for the development of a polysaccharide based colon delivery system for is the presence of large amounts of polysaccharidases in the human colon as it is inhabited by a large number and variety of bacteria which secrete many enzymes e.g. β-D-glucosidase, β-D-galactosidase, amylase, pectinase, xylanase, β-D-xylosidase, dextranase, etc.[25,26] The bacterial enzymes of colon degrades the carrier polymer and release the contents for localized and systemic absorption through colon.[27]

Table 3: Microbially degradable materials used for colonic delivery [28]

Class	Examples
Disaccharides	Lactose, Maltose
Oligosaccharides	Cellobiose, Cyclodextrin,Lactulose
Polysaccharides	Alginates**,** Amylose, Arabinogalactan, Cellulose, Chitosan, Dextran, Galactomannan, Inulin, Karaya gum, Pectin, Starch, Xylan, Xanthan and Tragacanth gum

b) pH sensitive polymer drug deliver to colon

pH sensitive drug delivery system (PSDDS) are gaining importance as these systems deliver the drug at specific time as per the pathophysiological need of the disease, resulting in improved patient compliance. PSDDS wherein the drug release is controlled primarily by the delivery system, stimuli induced PSDDS in which release is primarily controlled by the stimuli, such as the pH present in the intestinal tract. The pH range of fluids in various segments of gastrointestinal tract may provide environmental stimuli for responsive drug release.[29] Radiotelemetry shows the highest pH levels (7.5±0.5) in the terminal ileum. On entry into the colon, the pH drops to 6.4±0.6. The pH in

the mid colon is 6.6±0.8 and in the left colon 7.0±0.7. There is a fall in pH on entry into the colon due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides.[30]

Polymers used in pH sensitive drug delivery system:

Most commonly pH dependent coating polymers used are copolymers of acrylic and methacrylic acid esters which contains a low levels of quaternary ammonium groups- Eudragit RS (RS 100), Eudragit RL (RL 100), Eudragit L 100, Eudragit L 100-55 and Eudragit S 100, which dissolves at pH ranges from 5.5-7.0 and hence none of these polymers are suitable to be used alone for coating of dosage forms that would start releasing the drug at pH 6.5 although this has been generally accepted as the desired pH for colon targeted delivery.[31]

Table 4: Marketed products of pH dependent system [32]

Drug	Trade Name	Formulation
Mesalamine	Asacol	Eudragit S coated tablet
Mesalamine	Salofac	Eudragit L coated tablet
Mesalamine	Claversal	Eudragit L coated tablet
Budesonide	Entocort	Eudragit L coated beads

c) Delayed (Time Controlled Release System) release drug delivery to colon

There has always been a controversy about the usefulness of pH dependent polymers for colon targeted delivery due to high pH variability of GI tract. To overcome this problem time controlled systems are used along with pH dependent systems.[33] Time controlled delivery has been achieved by applying coats onto drug containing cores which delaying the release through different mechanisms or alternatively based on capsule-shaped and osmotic devices.[34] Enteric coated time- release press coated (ETP) tablet (fig. 1) are composed of three components i.e. a drug containing core tablets (rapid release function), the press coated swellable hydrophobic polymer layer (Hydroxy- propyl cellulose layer, time release function), and an enteric coating layer (acid resistance function). 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 occur.[23]

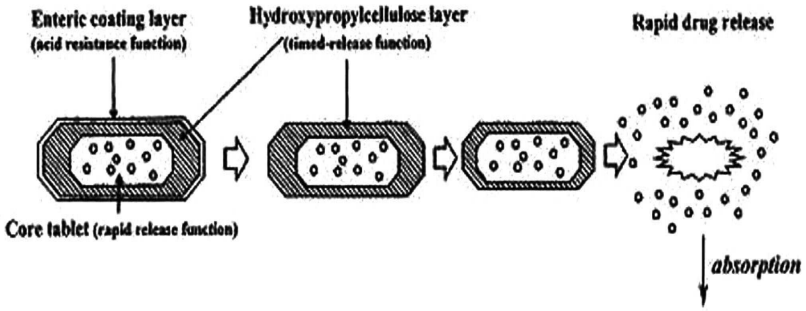

Figure 1: Design of enteric coated timed-release press coated tablet (ETP Tablet) [23]

(B) New drug approaches for colon targeting

a) Pressure controlled drug delivery system

GIT pressure is another mechanism that is utilized to initiate the release of the drug in the distal part of the gut. The muscular contraction of the gut wall generates this pressure which is responsible for the grinding and propulsion of the intestinal contents. The pressure generated varies in the intensity and duration throughout the GI tract while the colon is considered to have higher luminal pressure due to the process that occurs during stool formation. Capsule shells fabricated from a water insoluble polymer such as ethyl cellulose have been used for this purpose. [35] The delivery ability of a pressure- controlled colon delivery capsule (PCDC) containing caffeine as a test drug was evaluated after oral administration to healthy human volunteers. These kinds of PCDCs having different thickness of a water insoluble polymer membrane were prepared by coating the inner surface of the gelatin capsule with ethyl cellulose (EC).[36] Hu et al. used the biomagnetic measurement system (BMS) to estimate the GI transit characteristics of this system in healthy volunteers. It is found that the capsule reaches at the ascending colon 4 and 5 h after oral administration in two subjects while a model drug, caffeine, was first detected in the saliva of the same two subjects 6 and 5 h following oral administration, respectively.[37] PCDCs were prepared from capsular shaped suppositories, which were spray coated with ethanolic EC and using fluorescein (FL) as model drug and by employing a pharmaceutical coating machine, Hicoater-mini®. [38] All examples stated indicate that PCDCs were able to deliver the drug efficiently to the colon.

b) Osmotically regulated drug delivery system

A significant milestone in oral NDDS is the development of the osmotic drug delivery system, an innovative and highly versatile drug delivery system. Osmotic drug delivery system (ODDS) differ from diffusion- based system in that; the delivery of active agent (s) is driven by an osmotic gradient rather than the concentration of drug in the device.[39] Osmotic systems utilizes the principle of osmotic pressure for the delivery of drugs.. They are also known as gastrointestinal therapeutic system. Alza corporation of the USA was first to develop an oral osmotic pump and still they leading in this field with the technology named OROS [40]

Figure 2: CPOP tablet before and after dissolution studies [41]

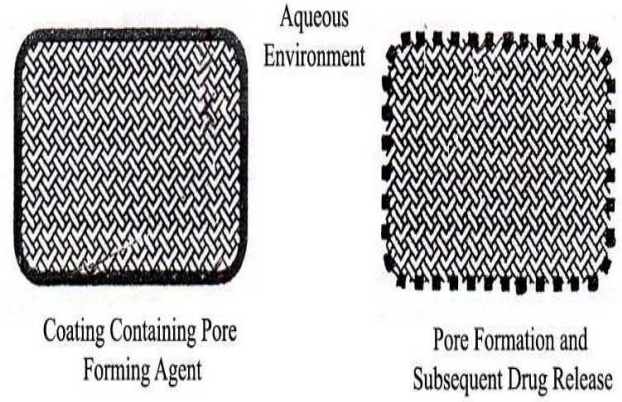

Table 5: Marketed products of different osmotic systems [42]

Product name	Active	Design	Dose
Acutrim	Phenylpropanolamine	Elementary pump	75 mg
Alpress LP	Prazosin	Push-Pull	2.5-5 mg
Covera HS	Verapamil	Push-Pull with time delay	180,240 mg
Ditropan CR	Oxybutinin chloride	Push-Pull	5,10 mg
Dynacire CR	Isradipine	Elementary pump	5,10 mg
Efidac 24	Pseudoephiderine	Elementary pump	60 mg IR,180 mg CR
Glucotrol	glipizide	Push-Pull	5,10 mg
Volmax	Salbutamol	Elementary pump	4,8 mg

Table 6: Principle of osmotically driven technologies and designs [43]

Technology	Developer	Description
Unitary-core		
(a) Elementary osmotic pump (EOP)	Alza corp., USA ADD Technology, CH	Single- drug composition compressed as a core surrounded by a semipermeable membrane with a drilled orifice EOP containing agents modifying the drug kinetics, such as
'Standard EOP'	Sun Pharma., India Alza Corp., USA	(i) a polymer or wax (ii) salts e.g. sodium chloride for salbutamol
Single composition osmotic tablet (SCOT)	Watson pharm./Andrx.USP Novartis Pharma., CH	EOP with highly porous membrane allowing high-drug loading (>75%) EOP with incorporated agent for modifying the drug thermodynamic properties (e.g. solubility) such as
Self –emulsified EOP	Ranbaxy, India Shire, USA Alza corp.,USA Supernus Pharm., India Alza corp.,USA	(i) crystal-habit modifying agents e.g. polymers (ii) complexing agent e.g. β-cyclodextrin (iii)surfactants e.g. sodium laurylsulphate (iv)pH-modifying agent e.g. acid or basic agent
Over-coated EOP	Osmodica, Arg	EOP surrounded by (i) an immediate release drug layer (DOEOP) (ii) entering coating (OROS-CT™) EOP containing sodium bicarbonate to promote the drug release
Effervescent EOP	Alza corp.,USA	EOP containing sodium bicarbonate to promote the drug release
(b) controlled porosity osmotic pump (CPOP)		
'Standard' CPOP	Alza corp., USA Merck & co.USA	Tablet-core surrounded by a membrane that allows the diffusion of the drug
Self-emulsified CPOP	Merck & co.USA	CPOP containing agents to modify the drug thermodynamics i.e. (i) complexing agent e.g. cyclodextrins (ii) pH – modifying agents
(ii) Multilayer osmotic pumps		
Push-pull osmotic pump (PPOP)	Alza corp., USA	Bi- or tri –layer tablet core composed by a drug layer to disperse the drug and a push –layer which generates a hydrodynamic pressure pushing the drug in one or more passageways
Push-stick osmotic pump (PSOP)	Alza corp., USA	PPOP improve to deliver high dose with both a sub-coating of the semipermeable membrane to avoid drug adhesion
Over-coated	Alza corp., USA	PPOP coated with enteric coating, delivering the

PPOP		drug without (OROS-CT™) or with a special onset (COER-24™)
Muco-adhesive osmotic system (MOTS)	Alza corp., USA	PPOP specially designed for buccal administration of tablet
(iii) Capsule-based osmotic pumps		
CHRONSET™	Alza corp., USA	System specially designed to deliver a bolus (>80% drug within 15 min) for intestinal or colonic absorption of protein or muco-adhesive particles
OSMET™	Alza corp., USA	Device designed to study the colonic absorption of the drugs delivering the drug as bolus or over a prolonged period upto 8 h
Asymmetric-membrane osmotic pump	Pfizer. USA	System coated subsequently with a semi permeable membrane and a highly porous membrane allowing higher water inflow
Liquid osmotic System (L-OROS™)	Alza corp., USA	Osmotic system delivering either liquid , lipid-lipid emulsion or solid dispersion

c) Novel Colon Targeted Delivery System (CODESTM)

CODESTM is a unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems.[3] . It is a 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 for site-specific drug release. The system consists of traditional tablet core containing lactulose, which is over coated with acid soluble material, Eudragit E and then subsequently overcoated with an enteric material, Eudragit L.[44]

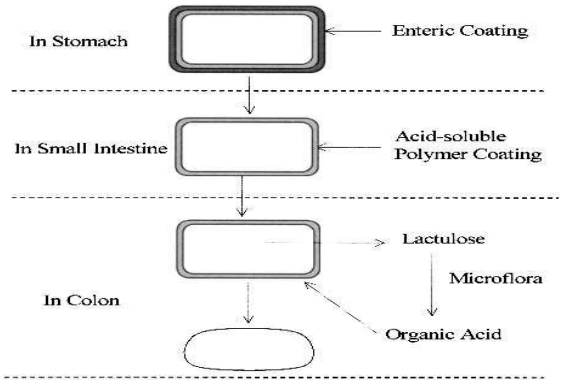

Figure 3: Systematical design of CODESTM [45]

The premise of the technology is that the enteric coating protects the tablet whilst 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 reaches at the colon, the lactulose within the tablet core ferments into short chain fatty acids which cause the Eudragit E coating to dissolve. This ultimately leads to the release of the contents of the tablet core in the colon.[3,45]

4. Other novel drug delivery system

Improvement in colonic drug delivery can be achieved by integrating different approaches into a single platform. For example to accelerate the enzymatically driven collapse of the carrier, an azo- dextran gel was suggested.[46] A new concept in colonic drug targeting using a combined pH- responsive and bacterial triggered drug delivery technology has been recently introduced. The combination of these independent but complementary release mechanisms should overcome the limitations of the single trigger systems and improve site specificity.[10] Bajaj amrita et al. prepared matrix system of tinidazole by using swellable and pH dependent polymers like hydroxypropyl methylcellulose (HPMC K4M and K 15 M) and Eudragit (Eudragit L-100 and S-100). These polymers used successfully in time and pH controlled approaches for colonic delivery.[47]

5. Conclusion

Since two decades, considerable amount of research work has been carried out in the area of colon targeting. CDDS offers considerable therapeutic benefits to patients in terms of both local and systemic treatment. Although the surface area in colon is low compared to small intestine, this is compensated by the markedly slower rate of transit. Various approaches described above are quite promising and further improvements are required to achieve the high bioavailability and safe delivery of drugs to the colon.

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Corresponding Author:

Sapna Saini*

M.Pharmacy(Pharmaceutics),

Email: *01sapnalongia@gmail.com*