

CONVENTIONAL AND NOVEL APPROACHES FOR COLON SPECIFIC DRUG DELIVERY: A REVIEW

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ABSTRACT

Lot of research is undergoing in colon specific drug delivery as this drug delivery route is not only useful for targeting the drugs required in the treatment of diseases associated with colon, but also as a potential site for the local and systemic delivery of peptide and proteins and other therapeutic drugs. Precise colon drug delivery requires the triggering mechanism in the delivery system that can respond only to the physiological conditions specific to the colon. The primary conventional approaches used to obtain colon-specific delivery were based on prodrugs, pH and time-dependent systems or microflora activated systems and achieved limited success. However, recently continuous efforts have been taken on designing colon-specific delivery systems with improved site specificity and versatile drug release kinetics to accomplish different therapeutic needs. The focus of this review is to provide detailed insight into the conventional as well as recent approaches used to target the therapeutic agents specifically to the colon.

Key words: Colon specific drug delivery, Pressure-controlled colon delivery capsules, CODES", Azo hydrogels

1. INTRODUCTION

2. Incorporating an existing medicine into a new drug delivery system can significantly improve its performance in terms of efficacy, safety and patient compliance. The need for delivering drugs to patients efficiently and with fewer side effects, there is need of development of new drug delivery systems. Colonic drug delivery refers to targeted delivery of drugs into the lower gastro intestinal tract (GIT), specifically in the large intestine (i.e., colon)^{1,2}. The GIT can be divided into five regions in terms of drug targeting: the oral cavity, esophagus, stomach, intestine, and the colon. Each of these regions may be further subdivided for specific targeted drug delivery³.

The colon is the uppermost portion of the large intestine, almost 5 feet from the start of the large intestine. The colon is a cylindrical tube lined by a moist, soft pink lining called mucosa; the pathway is called the lumen and is approximately about 15 cm

wide and may contain anywhere between 5 and 25 pounds of waste matter⁴. The cecum forms the first part of the colon and leads to the right colon or the ascending colon (just under the liver) followed by the transverse colon, the descending colon, sigmoidal colon, rectum, and the anal canal⁵. The structural features that distinguish colon from small intestine include the absence of villi. However, the intestinal surface of the colon is increased to approximately 1300 sq.cm, because of the presence of plicae semilunares, which are crescentic folds⁶. The proximal and distal colon differs in the absorption of drug at each site.

The major functions of the colon are:

- 1) The consolidation of the intestinal contents into feces by the absorption of the water and electrolytes and to store the feces until excretion. The absorptive capacity is very high; each day about 2000 mL of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed.
- 2) Creation of a suitable environment for the growth of colonic microorganisms, such as Bacteroides, Eubacterium, and Enterobacteriaceae.
- 3) Expulsion of the contents of the colon at a suitable time.
- 4) Absorption of water and Na^+ from the lumen, concentrating the fecal content, and secretion of K^+ and HCO_3^- .

The site specific delivery of drugs to the colon is valuable in the treatment of several colonic diseases like inflammatory bowel diseases (Crohn's disease and ulcerative colitis), irritable bowel syndrome and colon cancer. Other potential applications of colonic delivery include chronotherapy, prophylaxis of colon cancer and treatment of nicotine addiction^{1,2}. The most critical challenge in such drug delivery approach is to preserve the formulation and also preserve the drug from degradation, release and/or absorption in the upper portion of the GIT^{7,8}. To achieve successful colon targeted drug delivery, a formulation need to produce controlled release in the proximal colon. The drug formulations such as therapeutic proteins and peptides which are susceptible to chemical and enzymatic degradation in the upper GIT are suitable for colonic delivery⁹⁻¹¹. Proteins and peptides such as insulin, calcitonin, vasopressin and the novel peptides such as cytokine inhibitors and antibiotics (e.g. nisin) are delivered systemically via colonic absorption. The colon is rich in lymphoid tissues and uptake of antigen into mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery. There is also an increasing interest in the colonic delivery for improving the oral bioavailability of drugs whose metabolizing enzyme, cytochrome P450 3A class, is comparatively lower in the colonic mucosa than in the small intestine¹². Increasing bioavailability via a colonic formulation approach has also been found to be effective in minimizing unwanted side-effects¹³. Absorption of drugs via colonic delivery is desirable for chronotherapy as formulation present in the colon for longer time. Diseases such as asthma, hypertension, cardiac arrhythmias, arthritis or inflammation are affected by the circadian biorhythms and these diseases require night-time or early morning onset of drug action. It is therefore highly desirable to have a delayed-release delivery system that can provide nocturnal release of a drug, which in turn may provide considerable relief to the patients while they are resting⁷. Overall, colon offers distinct advantages on account of a near neutral pH, a much longer transit time, relatively low proteolytic enzyme activity and offers a much greater responsiveness to absorption enhancers as a site for drug delivery. All These characteristics make this distal part of GIT one of the most useful sites for the delivery of various drug molecules, including proteins and peptides. Colon-specific delivery systems prevent the release of the drug in the upper-

part of GIT and require a triggering mechanism to release the drug on reaching the colon.

1.1 Anatomy and physiology of the colon:

In terms of size and complexity, the human colon falls between that of carnivores which has no identifiable junction between ileum and colon, and herbivores which have a voluminous cecum. The human cecum is small and there is a rudimentary appendix. The human colon can be divided into three functional areas,

- The cecum and proximal colon, which act as a fermentation chamber,
- The transverse colon, the motor patterns of which may hold material in the proximal colon or propel it distally but that may also be an important site for the absorption of water and the rectum,
- Proximal colon acts as a reservoir for fecal material and allows defecation to be delayed until socially convenient¹⁴.

Region of GI Tract	Length (cm)	Internal Diameter (cm)
Entire GI Tract	500-700	
Small Intestine		3-4
Duodenum	20-30	
Jejunum	150-200	
Ileum	200-350	
Large Intestine	90-150	6
Cecum	6-7	
Ascending colon	20	
Transverse colon	45	
Descending colon	30	
Sigmoid colon	40	
Rectum	12	
Anal canal	3	

Table 1: Summary of anatomical and physiological regions of GI tract¹⁵.

The physiology of the proximal and distal colon differs in several respects that relate to their function and may affect drug absorption at each site. The physical properties of the luminal contents of the colon also changes from liquid in the cecum to semisolid in the distal colon. In addition to the site of the colon, there may also be differences in the environment of a drug or molecule depending on whether it is in the bulk phase or next to the mucosa, and whether it is free in the aqueous phase or bound to, or trapped in, solid material such as dietary fiber residues.

	Proximal	Distal
Function	Fermentation Chamber, absorption	Absorption, Storage
Innervation	Vagal/pelvic Splanchnic/lumbar Muscle more distensible	Pelvic, lumbar, greater Sensitivity to neural Stimulation
Blood supply	Superior mesenteric Artery and vein, Greater blood flow	Inferior mesenteric Artery and vein

Absorption	92% of chloride-dependent transport is electro neutral greater overall capacity	Chloride-dependent Transport mainly, Amiloride sensitive
Luminal contents	Liquid, lower pH (4.6-7.8), higher SCFA, very active bacterial metabolism	Semisolid, neutral pH, lower SCFA, lower bacterial activity.

Table 2: Major Difference between Proximal and Distal Colon

1.2 PARAMETERS FOR COLON SPECIFIC DRUG DELIVERY

1.2.1. Motility

Studies of colonic motility *in vivo* usually rely on measurement of changes in muscle electrical activity that may determine contractions. Manometer measure changes in colonic pressure caused by contractions and/or strain gauges measure contractions more directly. All approaches provide useful information but when used separately may not give a complete picture of colonic motor events. Electrical activity may not produce measurable contraction and manometric techniques can only detect contractions that occlude the lumen sufficiently to register as an increase in pressure. *In vitro* measurements using strips or segments of colon may suggest mechanisms and patterns of electrical and motor activity, but their role must be assessed *in vivo* in an intact colon with enteric and autonomic nervous system (ANS) and central nervous system (CNS) connection maintained. Since *in vivo* studies in human involve intubations and often bowel cleansing (sometimes with cathartics that may sensitize the colon), it is difficult to assess whether the same patterns would be seen without the invasive tubes and with a colon full of chemically and mechanically stimulating contents¹⁶.

1.2.2. pH in the Colon

The pH is different in the stomach, small intestine and colon and it depends upon factors such as diet, food intake, intestinal motility and disease states. This variability in the gastric pH makes it more challenging for the specialists working in this field to design a delivery system that would be robust enough to withstand these changes^{17,18}. The colonic drug delivery uses this variation in pH along the GIT to target the drug¹⁹. The pH gradient in GIT range from 1.2 in the stomach, 6.6 in the proximal small intestine to a peak of about 7.5 in the distal small intestine²⁰. The right, mid, and left colon have pH values approximately 6.4, 6.6 and 7.0 respectively. The pH of the colon is often lower than the pH of the small intestine, which is as high as 8 or 920. There is a fall in pH on the entry into the colon due to the presence of short chain fatty acids produced by bacterial fermentation of polysaccharides. This fall in pH has to be targeted to deliver the drug to the small intestine by the way of pH-sensitive enteric coatings²¹.

1.2.3. Colonic Microflora & Their Enzymes

Drug release in various parts of GIT depends upon the presence of intestinal enzymes that are derived from gut microflora residing in high numbers in the colon. These enzymes are used to degrade coatings/matrices as well as to break bonds between an inert carrier and an active agent (i.e., release of a drug from a prodrug) resulting in the drug release from the formulation. Almost 400 distinct bacterial species have been found, out of which 20% to 30% are of the genus *Bacteroides*⁴. The upper region of GIT consists of very small number of bacteria and predominantly gram-positive facultative bacteria. The concentration of bacteria in the human colon is around 1000 CFU/mL. The most important anaerobic bacterias are *Bacteroides*, *Bifidobacterium*,

Eubacterium, Peptococcus, Peptostreptococcus, Ruminococcus, Propionibacterium, and Clostridium²².

The GI microflora in the colonic region is used for drug release and which has great interest to researchers in recent times. The majority of bacteria in the GIT are present in the distal gut and remaining distributed throughout. Endogenous and exogenous substrates, such as carbohydrates and proteins, escape digestion in the upper GIT but are metabolized by the enzymes secreted by colonic bacteria²³.

Pectin and its combination with other polymers have been studied for colon-specific drug delivery. Pectin is needed in large quantities to control the release of the drug through the core when used alone. The tablets coated with composition of polymer such as pectin, chitosan and hydroxypropyl methylcellulose are passed intact through the stomach and small intestine and broke in the colon. This coating composition of a mixture was proven very efficient and beneficial^{23,24}. A summary of the most important metabolic reactions carried out by intestinal bacteria is provided in Table 3²⁵.

Enzymes	Microorganism	Metabolic Reaction Catalyzed
Nitroreductase	E. coli, Bacteroids	Reduce aromatic and heterocyclic nitro compounds
Azoreductase	Clostridia, Lactobacilli, E. Coli	Reductive cleavage of azo compounds
N-Oxide reductase, sulfoxide reductase	E. coli	Reduce N-Oxides and sulfoxides
Hydrogenase	Clostridia, Lactobacilli	Reduce carbonyl groups and aliphatic double bonds
Esterases and amidases	E. coli, P. vulgaris, B. subtilis, B. mycoides	Cleavage of esters or amidases of carboxylic acids
Glucosidase	Clostridia, Eubacteria	Cleavage of β -glycosidase of alcohols and phenols
Glucuronidase	E. coli, A. aerogenes	Cleavage of β -glucuronidases of alcohols and phenols
Sulfatase	Eubacteria, Clostridia, Streptococci	Cleavage of O-sulfates and sulfamates

Table 3: Various metabolic reaction and their enzymes.

1.2.4. Colon transit of the material

One of the major determinants for the absorption of a compound in colon is its residence time in any particular segment of the colon. The time taken for the food to pass through the colon is the transit time and in normal subjects it is about 78 hr for expulsion of 50% ingested material, but may range from 18 to 144 hr. Measurement of mean transit time after ingestion of material for several days give a steady-state transit time about 54.2 hr. Men had slightly shorter transit times than women and this was most apparent in more proximal colon²⁶. X-ray studies have the advantage that the colon is full of solid material and the subjects are on a normal diet²⁶. A rapid emptying of the proximal colon (88 mm) suggested that the transverse colon is a major storage site.

Gastric emptying of dosage forms is different and it depends upon the state of the

subject i.e. fed or fasted and the properties of dosage form such as size and density. The GIT transit times of different dosage forms are provided in Table 4.

Dosage Form	Transit Time (h)		
	Stomach	Small Intestine	Total
Tablets	2.7 ± 1.5	3.1 ± 0.4	5.8
Pellets	1.2 ± 1.3	3.4 ± 1.0	4.6
Capsules	0.8 ± 1.2	3.2 ± 0.8	4.0
Solution	0.3 ± 0.07	4.1 ± 0.57	4.4

Table 4: Transit times of various dosage forms across the segments of the GI tract²⁷.

Whole gut transit times was relatively long, ranging from 56 to 78 hours. Colonic transit times ranged from 50 to 70 hours²⁸.

1.3 Rational for the development of oral colon targeted drug delivery:

Oral delivery of therapeutic drugs has become a widely accepted route though GIT presents several formidable barriers to the drug delivery. During early stages of drug development, some new chemical entities (NCE's) present a challenge in efficacy testing due to their instability in gastric fluids and/or irritation in the GIT.

The colon targeted drug delivery is developed for the effective treatment of local pathologies, chronotherapy (asthma, hypertension, cardiac arrhythmias, 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 tissues.

Advantages:

1. Drugs are directly available at the target site.
3. Comparatively lesser amount of required dose.
4. Decreased side effects.
5. Improved drug utilization

6.1.4 General considerations for design of colonic formulations

The design of the colonic formulation is to provide a 'burst release'²⁹ or to sustain/prolong release once they reach the colon. The proper selection of a formulation approach is dependent upon several important factors like pathology and pattern of the disease (especially the affected parts of the lower GIT) or physiology and physiological composition of the healthy colon if the formulation is not intended for localized treatment, physicochemical and biopharmaceutical properties of the drug such as solubility, stability and permeability at the intended site of delivery and the desired release profile of the active ingredient. The pH gradient of the GIT is most important physiological factor considered in the design of delayed release colonic formulation. Drug dissolution and release rate of the drug in the colon are also taken into consideration in the formulation of colonic drug delivery³⁰. Generally, due to presence of less fluid in the colon than small intestine, the dissolution and release rate from colonic formulations is slow and this may in turn lead to lower systemic availability of the drugs. If the drug candidate is poorly water soluble then this issue could be more problematic and hence may require higher doses for therapy. Consequently, such drugs need to be delivered in a pre-solubilized form, or formulation should be targeted for proximal colon, which has more fluid than in the

distal colon³¹.

2. Conventional Pharmaceutical approaches for targeting drugs to the Colon:

1. □pH sensitive systems
2. Microbially triggered systems
 1. □Prodrugs
 2. Polysaccharide based systems
3. Timed release systems

2.1. pH sensitive systems:-

Coating is one of the simplest formulation technologies used for colon-specific delivery. Coating agents used in colon specific drug delivery are pH sensitive polymers. The dissolution performance of these polymers is influenced by pH. The polymer which contains ionizable phthalic acid group dissolves much faster at a lower pH than those with acrylic or methacrylic acid groups. The dissolution rate of Eudragit® is influenced in the presence of plasticizer³² and the nature of the salt in the dissolution medium³³⁻³⁵. The advantage of coated formulation is in terms of cost and ease of manufacturing. The coated formulations can be either a single-layered or a multi-layered product. The coating of single-layered product may be composed of a single enteric polymer that has a pH-dependent solubility or a mixture of two polymers one of which has pH-dependent while other have a pH independent solubility. For multi-layer products, the coating is applied in successive layers which could be either based on two enteric polymers that have different pH-dependent solubility profiles³⁶.

GI residence time of the dosage form is another important parameter for pH-dependent colon targeted drug delivery systems and is influenced by many physiological and other factors^{37,38}. There are standard GI residence values for various parts of the GIT³⁹. Most commonly used pH-dependent coating polymers are methacrylic acid copolymers. These polymers dissolve above pH 5.5 by forming salts and disperse in water to form latex and use of organic solvents in the coating process can be avoided. Eudragit® L100-55 is prepared in Eudragit® L30D-55 for a ready to use aqueous dispersion. The water solubility of the Eudragit® S depends on the ratio of free carboxyl groups to the esterified groups.

Polymers	Threshold pH
Eudragit® L 100	6.0
Eudragit® S 100	7.0
Eudragit® L-30D	5.6
Eudragit® FS 30D	6.8
Eudragit® L 100-55	5.5
Polyvinyl Acetate Phthalate	5
Hydroxypropyl Methylcellulose Phthalate	4.5- 4.8
Hydroxypropyl Methylcellulose Phthalate 50	5.2
Hydroxypropyl Methylcellulose Phthalate 55	5.4
Cellulose Acetate Phthalate	4.8
Cellulose Acetate Trimellate	5.0

Table 5: Commonly used Eudragit Polymer for pH dependent coating system⁴⁰

2.2 Microbially triggered systems

2.2.1. Prodrugs

A prodrug is a pharmacologically inactive derivative of a parent molecule that requires some form of transformation in vivo to release the active drug at the target site. The prodrug approach involves covalent linkage between the drug and its carrier so that upon oral administration the moiety remains intact in the stomach and small intestine. The triggering mechanisms for the release of the drug in the colon can be decided by the type of linkage that is formed between the drug and the carrier. The varieties of enzymes, mainly of bacterial origin present in the colon, are essential for the biotransformation of the prodrugs. The enzymes like azoreductase, galactosidase, xylosidase, nitroreductase, glycosidase and deaminase are mainly targeted for colonic drug delivery. The prodrugs are successful as colon drug carriers if they are hydrophilic and bulky as it minimizes their absorption from the upper GIT. Once the prodrug reaches to the colon, it is converted into a more lipophilic drug molecule that is then available for absorption. The drugs can be conjugated with different sugar moieties to form glycosidase linkage which due to their bulky and hydrophilic nature can not penetrate the biological membranes upon ingestion. The drugs are freed from the sugar upon break down by the action of glycosidase. Anaerobic microflora in the large bowel or exfoliated cells of the small intestine derived glycosidase activity in the GIT^{41,42}. Friend and Chang prepared dexamethasone-2-glucoside and prednisolone-2-glucoside for delivery of the steroids to the colon⁴³. The steroids in free form show maximum absorption when administered orally in the small intestine however, less than 1% of it reaches the colon. The membrane permeability of amino acids and proteins observed to be reduced due to the hydrophilic polar groups like -NH₂ and -COOH present in proteins. Non-essential amino acids such as glycine, tyrosine, methionine and glutamic acid conjugate with salicylic acid and these conjugates show more enzymatic specificity for hydrolysis by colonic enzymes leading to the minimal absorption and degradation in the upper GIT⁴⁴. Glucuronide and sulphate conjugation are the major mechanism for the inactivation and preparation for clearance of many drugs. Bacteria of the lower GIT secrete β -glucuronidase and can deglucuronidate a variety of drugs in the intestine⁴⁵. The azo linkage exhibits a wide range of thermal, chemical, photochemical and pharmaceutical properties. The intestinal bacteria can extensively metabolize azo compounds, by intracellular enzymatic components and extracellular reduction⁴⁶. The azo compounds can be used for coating the drug cores for the development of the colon targeting drug delivery systems⁴⁷. The use of sulphasalazine for the treatment of rheumatoid arthritis and inflammatory bowel disease (IBD) has an azo bond between 5-ASA and sulphapyridine⁴⁸. The cyclodextrin complexes are practically resistant to gastric acid and salivary and pancreatic amylases. The drugs stability and/or absorption performance can be enhanced by forming complexes with cyclodextrins^{49,50}. A clinical study has shown clear evidence that cyclodextrin complexes are poorly digested in the small intestine but are almost completely degraded by the colonic microflora^{51,52}.

2.2.2. Polysaccharides based systems

Polysaccharides are the polymers of monosaccharides which retains their integrity because they are resistant to the digestive action of gastrointestinal enzymes. The matrices of polysaccharides are assumed to remain intact in the physiological environment of stomach and small intestine; however, they are acted upon by the bacterial polysaccharidases once they reach in the colon resulting in the degradation

of the matrices. Natural polysaccharide polymers have an appeal to the area of drug delivery as they are comprised of polymers having a large number of derivatizable groups, a wide range of molecular weights, biodegradability, varying chemical compositions, a low toxicity yet high stability. They are already approved as pharmaceutical excipient. The number of polysaccharides such as amylose, guar gum, pectin, chitosan, inulin, cyclodextrins, chondroitin sulphate, dextrans and locust bean gum has been investigated for their use in colon targeted drug delivery systems⁵³⁻⁵⁵. The selection of a suitable biodegradable polysaccharide is the most important factor in the development of polysaccharide derivatives for colon targeted drug delivery.

2.3. Timed release systems

In these systems the release of the drug is decided by the transit time of a formulation in the GIT, which makes it challenging to develop a formulation that can achieve a precise drug release in the colon. The time release systems are designed in such way that the site of delivery (i.e. colon) is not affected by the individual's difference in the gastric emptying time, pH of the stomach and small intestine or the presence of anaerobic bacteria in the colon⁵⁶. On an average, an orally administered dosage form takes about 2 h in stomach and 3 h to travel through the length of the small intestine to the beginning of the colon⁵⁷. The small intestinal transit time is relatively consistent as compared to gastric emptying rate and a time release systems are dependent on it. By selecting a suitable combination of controlled-release mechanisms, the drug release from these systems can be precisely programmed to produce predetermined lag phase. In general, pH-dependent (enteric coat) components are used for time released formulations of colonic delivery because the transit of a formulation in the GIT is largely influenced by the gastric emptying time. In the time-release formulations, controlled release components based on mechanism of swelling (gelling), osmosis or a combination of two are often included.

Time released formulations are in the form of capsules and/or bilayered tablets. The balance between the tolerability and thickness of a water insoluble membrane and the amount of a swellable excipient such as low substituted hydroxypropyl cellulose (L-HPC) and sodium starch glycolate which controls the release time of the drug from formulations. The capsule shell of the formulation is made up of ethyl cellulose (EC) and it is approximately $120^{1/4}$ m in thickness, which contains micropores at the bottom of body. The filled material is a solid dispersion formulation of the drug. A capsule body is also made of EC and a tablet containing L-HPC made by direct compression⁵⁸ (Fig.1).

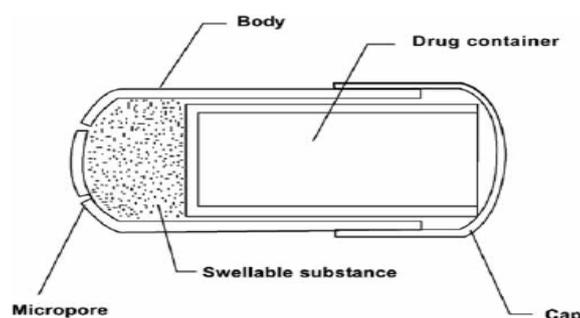


Fig 1: Time-controlled capsule for colonic delivery⁵⁹

GI fluid permeates through the micropores of the capsule shell and causes swelling of swellable excipients. This increases an inner pressure that pushes the drug container

leading to the breakdown of the capsule cap and disintegration of the capsules. The disintegration time of capsule depends upon the balance between the swelling pressure of formulated L-HPC and the strength and tolerability of the EC capsule⁵⁸.

3. Novel pharmaceutical approaches for targeting drugs to the colon:

1. Pulsatile

1. Pulsincap System
2. Port System
2. Pressure-controlled colon delivery capsules (PCDCs)
3. CODES
4. Osmotically controlled colon targeted drug delivery (OROC-AT)
5. Colonic drug delivery system based on pectin and galactomannan coating
6. Multiparticulate system based drug delivery
7. Azo hydrogels
8. Nanoparticles

3.1. Pulsatile colon targeted drug delivery:

3.1.1. Pulsincap® system

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 water-insoluble 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 time⁶¹.

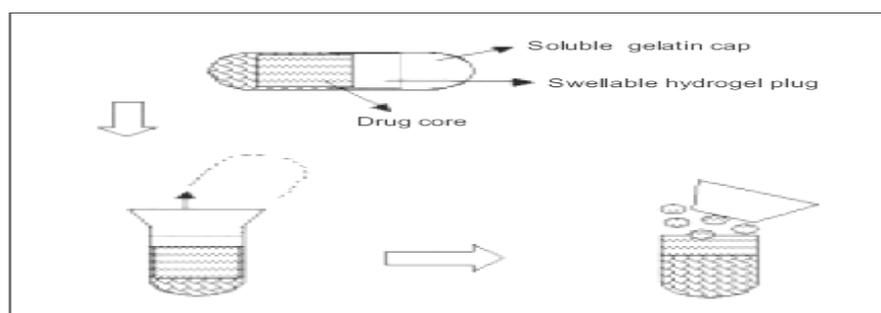


Fig. 2: Design of Pulsincap® system.

3.1.2. Port System

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 formulation⁶². 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 a

second no-release interval. Release of third dose occurs within 7-9 h of ingestion. This system avoids the second time dosing.

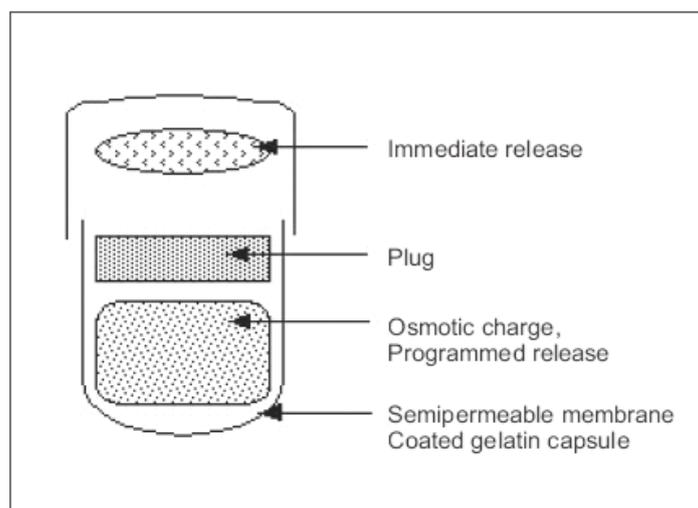


Fig. 3: Plan of Port® system.

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 varied⁶³⁻⁶⁵. 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-

- Extended daytime or nighttime activity
- Reduced side effects
- Reduced dosage frequency
- Reduction in dose size
- Improved patient compliance
- Lower daily cost to patient due to fewer dosage units are required by the patient in therapy.
- Drug adapts to suit circadian rhythms of body functions or diseases.
- Drug targeting to specific site like colon.
- Protection of mucosa from irritating drugs.
- Drug loss is prevented by extensive first pass metabolism⁶⁶.

In different body conditions, oral controlled drug delivery system with continuous release does not show suitability and may require pulsatile release of drug. A pulsatile release profile is characterized by a time period of no release (lag time) followed by a rapid & complete release of the drug from dosage form. Conditions requiring pulsatile release include– In the blood level hormones like rennin,

aldosterone & cortisol are daily fluctuated. Changes in many functions of the body like activity of liver enzyme, blood pressure, intra-ocular pressure etc occurs due to changes in the blood level of hormone which is generally known as circadian rhythm⁶⁷. Circadian rhythm also affects the pH, gastric acid secretion in stomach, gastric emptying and gastric intestinal blood transfusion⁶⁸. Various diseases are dependent on the circadian rhythm, like acute myocardial insufficiency that occurs mostly in the afternoon (around 4.00 p.m.) and epileptic seizures have the highest occurrence in the morning. These conditions demand consideration of diurnal progress of disease rather than maintaining constant plasma drug level. In these conditions, the release of drug from the delivery system is required during morning period although dose is administered at night. Time dependent delivery also required for the diseases like bronchial asthma, angina pectoris, rheumatic disease, ulcer & hypertension⁶⁹. Pulsatile release of drug is responsible for producing biological tolerance though continuous presence at the biophase is prevented by these systems. It releases drug after lag time (time at which drug is required by the body). The delivery system should prevent the release of drug in the upper 2/3rd portion of GIT for drugs required to be targeted in colonic region (distal organ)^{70,71}. Pulsed fashion can be achieved by the enteric coating of the delivery system⁷².

All above conditions requires chronotherapeutics (i.e. precisely time therapy) and this objective can be accomplished with chronotherapeutics where right amount of the drug is released at the right time using time controlled pulsatile drug delivery devices.

3.2. Pressure-controlled colon delivery capsules (PCDCs)

The contractile activity of the stomach is required for digestion within the GIT and peristaltic movements responsible for propulsion of intestinal contents. The movement from one part to the next part of large intestine, from the ascending to the transverse colon, by forcible peristaltic movements commonly termed as mass peristalsis. The peristaltic waves occur only three to four times a day. The temporarily increase the luminal pressure within the colon is because of these waves and it only forms the basis for the design of pressure-controlled systems. Intestinal pressure-controlled colon delivery capsules (PCDCs) has inner surface of the gelatin capsules coated with water insoluble polymer, ethylcellulose (EC)^{73,74} and the drug was introduced along with the suppository base. The thickness of the EC membrane of PCDCs determines the disintegration characteristics. In PCDCs, the drug is dissolved with a suppository base. The system behaves like an EC balloon containing drug solution after administration as suppository base dissolves at body temperature. The viscosity of luminal content increases due to reabsorption of water in the colon⁷⁵. Increased intestinal pressures directly affect the system via colonic peristalsis (highamplitude propagated contractions). The release of drug load in the colon from PCDCs due to raised pressure. Hence, the thickness of EC membrane plays an important role in the colon delivery of drugs for colon specific diseases as well as protein drugs. However, it should be noted that our understanding of this raised pressure phase is very limited. It was reported that this pressure can be as high as 110 mm of Hg with duration of 14s in healthy subjects^{76,77}, however this activity follows the circadian rhythm, with the occurrence frequency of maximum after waking, after meals or with defecation⁷⁷. Based on limited *in vivo* evaluation⁷⁸, the performance of this system appears to be dependent on the capsule size and the thickness of EC coating. Hu et al., used the biomagnetic measurement system (BMS) to estimate the GI transit characteristics of this system in healthy volunteers⁷⁹. It was found that the

capsule arrived 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 at 6 and 5 h following oral administration, respectively. This indicated that PCDCs delivered the drug to the colon.

3.3. CODES™ technology

To avoid the inherent problems associated with pH- or time dependent systems the CODES™ technology was designed for colon-specific drug delivery^{80,81}. The CODES™ 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 CODES™ consists of a core tablet coated with three layers of polymer coatings as schematically presented in Fig 4.

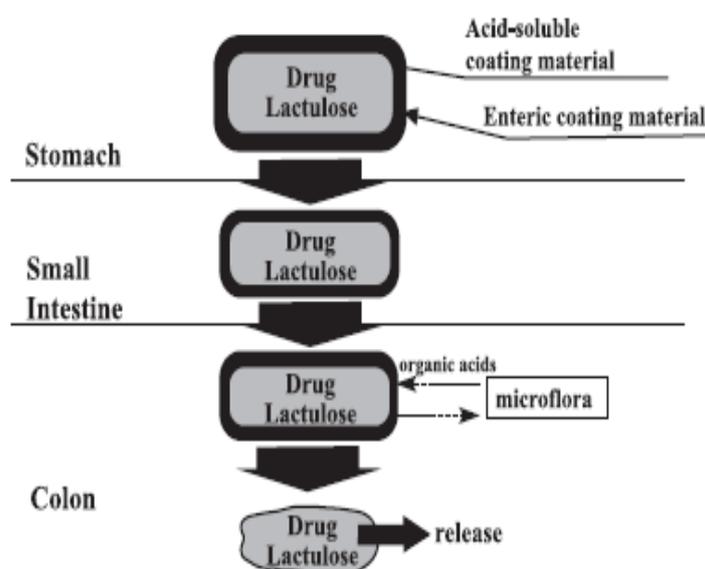


Fig 4: Schematic of the CODES™ formulation⁸².

The outer coating is composed of a standard enteric polymer such as Eudragit® L. Once the unit passes through the pyloric and into the duodenum, this coating dissolves exposing the undercoating, which is composed of Eudragit® E. This coating will not dissolve in the environment of the small or large intestine. The undercoating permits lactulose to be released into the environment adjacent to the tablet. This disaccharide is then metabolized to short chain fatty acids that lower the local pH to the point where the Eudragit E dissolves. This final dissolution step exposes the core of the tablet permitting drug dissolution to occur. Any possible interactions between the oppositely charged polymers can be prevented by first coating (next to the core tablet) using an acid-soluble polymer (in the present case, Eudragit E® was used) and outer enteric coating. The core tablet is comprised of the active, one or more polysaccharides and other desirable excipients. The polysaccharides degradable by enterobacteria to generate organic acid include mannitol, maltose, stachyose, lactulose, fructooligosaccharide etc. During its transit through the GIT, CODES™ remains intact in the stomach due to the enteric protection which will dissolve in the small intestine as the pH is above 6. Upon entry into the colon, the polysaccharide

inside the core tablet will dissolve and diffuse through the coating. The bacteria will enzymatically degrade the polysaccharide into organic acid. This lowers the pH of the surrounding system and result in the dissolution of the acid-soluble coating and subsequent drug release.

3.4. Osmotically controlled colon targeted drug delivery

The Osmotically controlled drug delivery system can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption.

OROC-CT (Alza Corporation)

The OROC-CT system can be single osmotic unit or may incorporate as many as 5-6 push pull units⁸³, each 4mm in diameter, encapsulated with in a hard gelatin capsule Fig 5. Each bilayer push pull unit surrounded by a semipermeable membrane which contains an osmotic push layer and a drug layer.

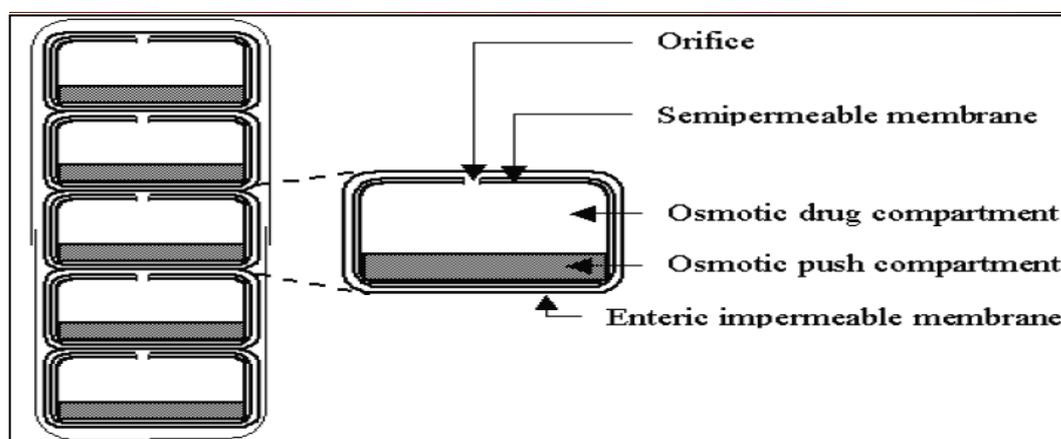


Fig 5: OROC-CT colon targeted drug delivery

An orifice is drilled through the membrane next to the drug layer. The gelatin capsule containing the push-pull units dissolves immediately after the OROC-CT is swallowed. Because of enteric coating of formulation, each push pull units is prevented from absorbing water in the acidic aqueous environment of the stomach and hence no drug is delivered. As the units reach the small intestine, the coating of the unit get dissolve in this higher pH environment ($\text{pH} > 7$), water enters the unit, causing the osmotic push compartment to swell and concomitantly creates a flowable gel in the drug compartment. The rate of water transport through the semipermeable membrane is precisely controlled for swelling of the osmotic push compartment forces drug gel out of the orifice. 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 from the unit begins as it reaches the colon. The OROS-CT units can deliver drug at constant release for up to 24 h in the colon and can over an interval as short as 4 h.

3.5. Colonic drug delivery system based on pectin and galactomannan coating:

This system consists of a conventional tablet or capsule coated with two specific polysaccharides, namely pectin and galactomannan. Though, individually neither pectin nor galactomannan used as a drug carrier for colon-specific delivery due to their high water solubility/swelling characteristics, however, the coating produced

from the mixture of the two polysaccharides shows solubility depending upon the pH of the coating solution. The coating from a pH 7 aqueous solution of pectin and galactomannan was shown to be strong, elastic and insoluble in simulated gastric and intestinal fluids. Accordingly, the coating of such polymer could protect drug from being released in the upper GIT. On the other hand, the coating from the identical solution with pH 7 observed to dissolve readily in the simulated intestinal fluids. Even though the mechanism of this observation remains to be investigated, it was proposed that due to the hydrogen bonding, hydrophobic force and the formation of an inter junction zone a complex between the two polysaccharides that might have been formed at pH 7 that lead to conformational changes in polysaccharides at the higher pH. Results indicated that the bacterial degradability of films produced by this method was still preserved in the colon. It was also demonstrated that the extent of film resistance to hydration and subsequent solubilization, the rate of film degradation by enzymes and the resultant drug release rate depend on the ratio of pectin to galactomannan. Higher percentage of galactomannan results in decreased bacterial degradation in the colon and prolonged duration of action and also of negligible drug release in the upper GIT. The site specificity of drug release was pharmacoscintigraphically confirmed in human subjects^{84,85}. Compared with the combination of pectin and EC⁸⁶ or amylose and EC⁸⁷, this technology might have the advantage of faster degradation *in vivo* since both pectin and galactomannan are readily degraded by the colonic microflora.

3.6. Multiparticulate system based drug delivery

Recently, much emphasis is being laid on the development of multiparticulate dosage forms in comparison to single unit systems because of their potential benefits like increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying⁸⁸. Multiparticulate approaches tried for colonic delivery includes the formation of pellets, granules, microparticles and nanoparticles. The use of multiparticulate drug delivery system is preferred to single unit dosage forms as it has been observed that multiparticulate systems enabled the drug to reach the colon quickly and were retained in the ascending colon for a relatively long period of time⁸⁹. These systems are capable of passing through the GIT easily due to their smaller particle size as compared to single unit dosage forms, leading to less inter- and intra subject variability. Moreover, multiparticulate systems tend to be more uniformly dispersed in the GIT that ensures more uniform drug absorption⁹⁰⁻⁹². Most commonly studied multiparticulate systems for colon specific drug delivery include pellets, granular matrices, beads, microspheres, and nanoparticles⁹³⁻⁹⁷.

Approaches for designing of multiparticulate system for colon targeted drug delivery
pH- and time- dependent systems⁹⁸

Microbially controlled systems⁹⁹

Microparticulate systems^{100,101}

Nanoparticulate systems¹⁰²⁻¹⁰⁴

3.7. Azo hydrogels

The synthesis and characterization of a series of novel azo hydrogels for colon-targeted drug delivery have been described¹⁰⁵⁻¹⁰⁷. The presence of pH-sensitive monomers and azo cross-linking agents in the hydrogel structure produces colon-specificity to the formulation. As these hydrogel travels through the GIT their

swelling capacity increases as the pH increases, being highest around pH 7.4. The drug entrapped in the hydrogel is released by the progressively degradation of hydrogel network via the cleavage of the cross-links. For the preparation of hydrogel systems different synthetic approaches were developed and it has been reported that they can be obtained by cross-linking polymerization of N-substituted (meth)acrylamides, N-tert-butylacrylamide and acrylic acid with 4,4'-di(methacryloylamino) azobenzene, 4,4'-di(N-methacryloyl-6-aminohexanoylamino) or 3,3',5,5'-tetrabromo-4,4',4',4'-tetrakis(methacryloylamino) azobenzene as the cross linking agents^{105,106}. An alternative approach for hydrogel preparation is cross-linking polymeric precursors. In this case, a reactive linear polymeric precursor was first prepared by copolymerization of N,N-dimethacrylamide, N-tert-butylacrylamide, acrylic acid, and N-methacryloylglycylglycine p-nitrophenyl ester. The precursors were then cross-linked with N,N'(aminocaproyl)-4,4'-diaminoazobenzene on the nitrophenyl ester to form the hydrogel structure¹⁰⁷. The hydrogels were also prepared by polymer-polymer reaction using the same polymeric precursor with the corresponding copolymer containing side chains terminating in NH₂ groups. Both *in vitro* and *in vivo* study shows the degradability of these hydrogels which has been well characterized. The degradation rate of hydrogel was associated with the equilibrium degree of swelling and being inversely proportional to the crosslinking density. Preliminary studies in rats indicated that the enzymatic degradation of the hydrogel occurred over several days to make this approach more effective for colon specific delivery¹⁰⁶.

3.8. Nanoparticles

Today, a vast number of investigations have been focused on nanoparticles and their role as drug delivery vehicles. Nanoparticles were first introduced in the mid seventies by Birrenbach and Speiser¹⁰⁸. The preparation of nanoparticles was simple, the particles formed were relatively stable and easily freeze-dried and hence biodegradable polymers were found useful and further developed for drug delivery. Nanoparticles are expected to become drug carriers for achieving oral peptide delivery. Because of polymeric nanoparticles have the advantages of protecting the protein and peptide drugs from chemical and enzymatic degradation in the GIT, increasing their stability and absorption across the intestinal epithelium as well as controlling the drug release¹⁰⁹⁻¹¹². A number of techniques such as polymerization, nanoprecipitation, inverse microemulsion can be used to prepare polymeric nanoparticles, however most of these methods involve the use of organic solvents, heat and vigorous agitation which may be harmful to the peptide and protein drugs^{113,114}. More recently the ionic gelation technique is used as the most favorable method for producing peptide and protein nanoparticles. The nanoparticles prepared by this method have a suitable size and surface charge, spherical morphology as well as a low polydispersity index indicative of a homogenous size distribution. The non usage of organic solvents, sonication or harsh conditions during preparation reduces the damage to the peptide and proteins and makes this method favorable for the preparation of protein loaded nanoparticles^{115,116}. Chitosan nanoparticles with excellent biodegradable and biocompatible characteristics have been used extensively as drug delivery vehicles¹¹⁷. However, due to poor solubility of chitosan at pH above 6.0, its quaternized derivatives such as trimethyl chitosan, triethyl chitosan, diethylmethyl chitosan and dimethylethyl chitosan, which are soluble at the intestinal pH, have been used to prepare nanoparticles loaded with insulin¹¹⁸⁻¹²¹. Chitosan

nanoparticles loaded with insulin were prepared by mixing positively charged polymer with the negatively charged insulin and nanoparticle formation occurred via electrostatic interaction. Studies have shown that insulin in nanoparticulate form was more likely to be delivered across the GIT than in its free soluble form¹²²⁻¹²⁴. The particle size and surface charge are critical factors in nanoparticle absorption. Size is a determining factor for both uptake and biological fate of the particulate systems. Moreover, a size dependent phenomenon exists in the gastrointestinal absorption of the particles. Studies have shown that particles with a size of 100 nm were taken up 6-times more than particles with 100 μ m by the absorptive cells¹²⁵⁻¹²⁷. Hydrophobic particles are absorbed more readily than hydrophilic ones. Thus increasing the hydrophobicity of particles may enhance their permeability through mucus but decreases the translocation through and across the absorptive cells¹²⁸. In the GIT, the particles interact with the mucus before coming in contact with the absorptive cells. Positively charged particles are more prone to uptake as they can associate with the negatively charged functional groups in the mucus¹²⁹. Accordingly, biodegradable hydrophobic nanoparticles with sizes between 100-200 nm and positive surface charge may be good candidates for uptake by the epithelial cells. The disadvantage of the nanoparticles is their bigger size in comparison to the soluble protein molecules and the fact that a lot of particles may get trapped inside the cells within the cellular membrane such as the Golgi apparatus or the endoplasmic reticulum being unable to pass across the cells intactly. Accordingly, while the use of nanoparticles is highly recommended for gene therapy their use for peptide drug delivery and absorption is debatable also with respect to the minimal drug load they can carry with them in comparison to bigger particles. Even though all of the above mentioned delivery systems gave reasonable results when studied *in vitro* and *ex-vivo*, they were only tested *in vivo* using small animals such as mice and rats with intestinal diameters much less than that of humans. For a delivery system to be useful for commercialization it must have reasonable bioavailabilities in bigger animals such as pigs or dogs with intestinal diameters closer to that of the humans. The small intestinal diameter of smaller animals allows the delivery system to easier come in direct contact with the intestinal wall where in bigger animals and humans reaching the absorbing surface still with full mucoadhesiveness is a big challenge. Moreover, the amount of mucus produced in bigger animals is higher than in the GIT of smaller animals. It was shown for nanoparticles developed by Peppas et al. that they lose their mucoadhesive properties in contact with soluble mucins present in the GIT of larger animals before reaching the absorbing surface and are no longer able to open the tight junctions and allow for the paracellular transport of the drugs¹³⁰.

4. CONCLUSION

A successful colon drug delivery requires triggering mechanism for the successful delivery to the colon. Few mechanisms have been incorporated into a delivery system to affect colon specific drug release due to the lack of discontinuity in physiological parameters along the GIT. So far, four approaches were proposed for colon-specific drug delivery: prodrugs, pH- and time-dependent systems and microflora activated systems. Among the four approaches, microflora-activated system appears more promising since there is an increased amount of bacterial population and associated enzyme activity in the colon represent a non-continuous event, independent of GI transit time. Compared with the colon-specific drug delivery systems previously reported, the recently designed systems discussed in the present article exhibit the

advantages like feasible processing, site specificity of drug release, usage of commonly used pharmaceutical excipients and versatile drug release kinetics, if so desired.

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