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REVIEW ON ADVANCES IN COLON TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT

The colon is the terminal part of the GIT which has gained in recent years as a potential site for delivery of various novel therapeutic drugs, i.e. peptides. However, colon is rich in microflora which can be used to target the drug release in the colon. Colon is a site where both local and systemic drug delivery can take place. Local delivery allows the topical treatment of inflammatory bowel disease. If drug can be targeted directly into the colon, treatment can become more effective and side effects can be minimized. These systemic side effects can be minimized by primary approaches for CDDS (Colon specific drug delivery) namely prodrugs, pH and time dependent systems and microbially triggered system which gained limited success and have limitations as compared with recently new CDDS namely pressure controlled colon delivery capsules (PCDCS), CODESTM (Novel colon targeted delivery system) osmotic controlled drug delivery system, Pulsincap system, time clock system, chronotropic system. This review is to understand the pharmaceutical approaches to colon targeted drug delivery systems for better therapeutic action without compromising on drug degradation (or) its low bioavailability.

INTRODUCTION: Drug delivery to colon can be achieved by oral and related routes. Rectal dosage forms (enemas and suppositories), are not always much effective due to high variability in the drug distribution by this route [1]. Therefore, the oral route is the most preferred. Conventional oral formulations dissolve in the stomach or intestine and are absorbed from these regions. The major obstacle with the delivery of drugs by oral route to the colon is the absorption and degradation of the drug in the upper gastrointestinal tract (GIT) [2].

Targeted drug delivery to colon is highly desirable for the local treatment of variety of bowel disorder [3-6]. Colon specific drug delivery system (CDDS) refers to delivery of drug into the lower gastrointestinal tract, which occurs primarily in large intestine (i.e. colon).[7] CDDS should be capable to protect drug from undergoing any chemical and therapeutic changes in the organs apart from colon. Colon mucosa with lesser intensity and lower proteolytic activity makes an appropriate site for the absorption of peptide and the protein drugs [8-10]. The colon has longer residence time i.e. up to 5 days which enhances the absorption of poorly absorbed drugs [11-13].

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CDDS overcomes the hydrolysis and enzymatic degradation in duodenum and jejunum and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability [14]. The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery. The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability.

This region of the colon is recognized as having a somewhat less hostile environment with less diversity and intensity of activity than the stomach and small intestine. Apart from retarding or targeting dosage forms, a reliable colonic drug delivery could also be an important starting position for the colonic absorption, undigested, unchanged and fully active peptide drugs [15]. The colon is having high water absorption capacity, the colonic contents are considerably viscous and their mixing is not efficient, thus availability of most drugs to the absorptive membrane is low. The human colon has over 400 distinct species of bacteria as resident flora, a possible population of up to 1010 bacteria per gram of colonic contents.

Among the reactions carried out by these gut flora are azoreduction and enzymatic cleavage i.e. glycosides [16]. These metabolic processes may be responsible for the metabolism of many drugs and may also be applied to colon-targeted delivery of peptide based macromolecules such as insulin by oral administration. Target site, colonic disease condition, and drugs used for treatment are shown in **table 1** [17].

TABLE1: COLON TARGETING DISEASES, DRUGS AND SITES

Target site	Disease condition	Drug
Topical action	Inflammatory bowel disease, Irritable bowel disease and Crohn's disease. Chronic pancreatitis	Hydrocortisone, Budesonide, Prednisolone, sulfaselazine, Olsalazine, Mesalazine, Balsalazide
Local action	Pancreatactomy and cystic fibrosis, colorectal cancer	Digestive enzyme supplements, 5-flourouracil
Systemic action	To prevent gastric irritation	NSAIDS
	To prevent first pass metabolism of orally ingested drugs	Steroids
	Oral delivery of peptides	Insulin
	Oral delivery of vaccines	Typhoid

Need of Colon Targeted Drug Delivery:

- Colon targeted drug delivery is needed to ensure the direct treatment at disease site, lower dosing and lesser systemic side effect.
- Colon-specific formulation could be used for prolong drug delivery.
- It should be considered as beneficial in the treatment of colon diseases.
- The colon is a site where both local or systemic drug delivery could be achieved.
- A number of other serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon.
- Formulations for colonic delivery are also suitable for delivery of drugs which are polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides [18].

Advantages of CDDS over Conventional Drug Delivery:
Chronic colitis, namely ulcerative colitis, and Crohn's disease are currently treated with glucocorticoids, and other anti-inflammatory agents. Administration of glucocorticoids namely dexamethasone and methyl prednisolone by oral and intravenous routes produce systemic side effects including adenosuppression, immunosuppression, cushinoid symptoms and bone resorption. Thus selective delivery of drugs to the colon could not only lower the required dose but also reduce the systemic side effects caused by high doses [19].

Criteria for selection of drugs for Colon Specific Drug Delivery Systems: Drugs which show poor absorption from the stomach or intestine including peptide are most suitable for CDDS. The drug used in treatment of inflammatory bowel disease (IBD), ulcerative colitis, diarrhoea and Colon cancers are ideal candidates for local colon delivery. The criteria for selection of drug for, CDDS are summarized in **Table 2.**

TABLE 2: CRITERIA FOR SELECTION OF DRUG FOR CDDS

Criteria	Pharmacological class	Non-peptide Drugs	Peptide drugs
Local effect in colon against GIT disease	Anti-inflammatory drugs	Oxyprepnolol, Nifidipine, Metoprolol	Antisense oligonucleotide, amylin
Colon cancer	Anti-neoplastic drugs	Pseudoephedrine	Glucagon, Epoetin
Drugs for targeting	Antiarthritic and Antiasthmatic drugs	Hydrocortisone,5-amino salicylic acid, prednisolone	Somatropin, Urotoilitin
Drugs undergo first pass metabolism	nitro-glycerine	Bleomycin , nicotine	Protirelin, Sermorelin
Drugs poorly absorbed from upper GIT	Antianginal and antihypertensive drugs	Isosorbide, Theophylline, Ibuprofen	Cyclosporine, Desmopressin
Dugs that degrade in stomach and intestine	Peptides and proteins	5- fluorouracil, doxorubicin	Insulin, Interferon, Gonadoreline

Drug carrier: Drug carrier is another factor which influences CDDS. The selection of carrier for particular drug depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. Factors such as chemical nature, stability and partition coefficient of the drug and type of absorption enhancer influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule. For example, aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond. The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the release properties and efficacy of the systems [23].

Factors that influence oral colon specific drug delivery systems

Gastric emptying time: This is affected by the state of fed or fast, size and caloric content of the ingested food.

Small intestine transit time: The mean transit time of the dosage form is about 3-4 hours to reach the ileocecal junction and the time period is consistent. It is rich in digestive enzyme, such as esterase, lipase, amylase, protease and glycosidase.

TABLE 3: GASTROINTESTINAL TRANSIT TIME OF CONTENTS

Organ	Transit time(hrs)
Stomach	<1(fasting), >3(fed)
Small intestine	3-4
Large intestine	20-30

Ileo-cecal junction (I.C.J) lag time: Highly variable, and hold up may occur for several hours.

Colonic transit: Show considerable variability between individual can be as high as 2-3 days.

Gastrointestinal pH profile [24]:

- Stomach pH 1- 1.5
- Small intestine pH 5-7.5
- Ascending colon pH 6.3 ± 0.58
- Transverse colon pH 6.6 ± 0.83
- Descending colon pH 7.04± 0.67

Gastrointestinal microflora:

- Stomach (<1000 CFU/ml)
- Small intestine (103-104 CFU/ml)
- Colon (1011-1012 CFU/ml) 400 species and most of them are anaerobes and Bacteroides.

Enzymatic Activity: Colon lumen contains 80% less enzymatic activity than small intestine. The large intestine is relatively free of peptidases so colon targeted delivery systems will be absorbed after peroral application [25]. The activity of the cytochrome P450 3A class is found lower in the mucosa of the colon than the small intestine.

So colon targeted delivery may direct to prominent plasma levels and improved oral bioavailability for drugs which are enzyme substrates. Examples of drugs that are absorbed from the colon include cefimetazole, 5-fluorouracil, cephradine, riboflavin, L-carnitine, theophylline, naproxen, oxyprepnolol, nifidipine and indomethacin [26-32].

Approaches For Colon Targeted Drug Delivery (CDDS): In colon-specific drug delivery system can be designed on the basis of following mechanisms with varying degrees of success;

1**. Primary approaches for CDDS**

a) pH dependent polymer coated drug delivery to the colon

b) Time controlled release system

c) Microbially Triggered Drug Delivery to Colon

d) Prodrug Approach for Drug Delivery to Colon

e) Polysaccharide based approach

2. **Newly Developed Approaches for CDDS**

a) Pressure controlled drug delivery system

b) Novel Colon Targeted Delivery System (CODESTM)

c) Osmotic controlled drug delivery system (OROS-CT)

d) Pulsincap System

e) Port system

f) Time clock system

g) Chronotropic system

Colonic delivery systems are also suitable for delivery of the drugs which are polar and/or susceptible to chemical and enzymatic degradation in the upper part of GI tract, in particular, therapeutic proteins and peptides e.g. insulin, calcitonin and vasopressin may be delivered systemically through colonic absorption. Another example includes peptides such as cytokine inhibitors and antibiotics, used in the treatment of inflammatory bowel diseases and GI infections, respectively. Apart from protecting these labile molecules, colon also offers an opportunistic site for oral delivery of vaccines because it is rich in lymphoid tissue. Therefore, the uptake of antigens through the colonic mucosa may lead to rapid and local production of antibodies. There is also an increasing interest in the colonic delivery for improving the oral bioavailability of drugs that are substrates of metabolizing enzymes is comparatively lower in the colonic mucosa than in the small intestine. Increasing bioavailability via a colonic formulation approach has also been found to be effective in minimizing unwanted side-effects. Drug release from this system is triggered by colonic microflora coupled with pH sensitive polymer coatings [33].

1) Primary Approaches for CDDS

a) **pH dependent polymer coated drug delivery to the colon:** In these system, drug can be formulated as solid dosage forms such as tablets, capsules, and pellets and coated with pH sensitive polymers as enteric coated. The pH of human GIT increases progressively from the stomach pH 1-2 which increases during fasting [34-37]. In the stomach, pH is between 1 and 2 during fasting but gradually increases after eating [38]. The pH is 6.5 in the proximal part of small intestine and 7.5 in the distal part of small intestine [39]. From the ileum to the colon pH decreases significantly. It is about 6.4 in the cecum. However, pH values as low as 5.7 is measured in the ascending colon [40].

The pH in the transverse colon is 6.6, in the descending colon 7.0. Use of pH-dependent polymers is based on this differences in pH levels. The pH dependent polymers in colon drug delivery are insoluble at low pH but become increasingly soluble as the pH increases [41]. A pH-dependent polymer protects the formulation in the stomach and proximal part of the small intestine, it may start to dissolve in the lower part of small intestine, and the site-specificity of formulations can be poor [42]. The decline in pH from the end of the small intestine to the colon can also result in problems, lengthy lag times at the ileo-cecal junction or rapid transit through the ascending colon which can also result in poor site-specificity of enteric-coated single-unit formulations [41].

TABLE 4: VARIOUS PH DEPENDENT COATING POLYMERS [43]

POLYMER	THRESHOLD pH
Eudragit L 100	6.0
Eudragit s 100	7.0
Eudragit® L-30D	5.6
Eudragit® FS 30D	6.8
Hydroxypropylmethylcellulose phthalate 50	5.2
Hydroxypropylmethylcellulose phthalate 55	5.4
Cellulose acetate trimellate	4.8

b) **Time Controlled Release System:** It is also known as pulsatile release, delayed or sigmoidal release system. Time-controlled systems are useful for synchronous delivery of drug either at pre-selected site of GIT tract. These systems are particularly useful in the therapy of disease, which depends on circadian Rhythms. Time – controlled formulations for colonic delivery are based on the principle of delaying the release of drug until it enters into the colon.

Time controlled release system (TCRS) such as sustained or delayed release dosage forms are also very promising drug release systems. However, due to potentially large variations of gastric emptying time of dosage forms in humans, in these approaches, colon arrival time of dosage forms cannot be accurately predicted, resulting in poor colonial availability [44]. The dosage forms may also be applicable as colon targeting dosage forms by prolonging the lag time of about 5 to 6 h. However, the disadvantages of this system are:

I. Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.

II. Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug [45].

III. Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhea, and the ulcerative colitis [46-47].

Therefore, time dependent systems are not ideal to deliver drugs to the colon specifically for the treatment of colon related diseases. Appropriate integration of pH sensitive and time release functions into a single dosage form may improve the site specificity of drug delivery to the colon. Since the transit time of dosage forms in the small intestine is less variable i.e. about 3±1 hr [48]. The time-release function (or timer function) should work more efficiently in the small intestine as compared the stomach. In the small intestine drug carrier will be delivered to the target side, and drug release will begin at a predetermined time point after gastric emptying.

On the other hand, in the stomach, the drug release should be suppressed by a pH sensing function (acid resistance) in the dosage form, which would reduce variation in gastric residence time [45]. Enteric coated time-release press coated (ETP) tablets, are composed of three components, a drug containing core tablet (rapid release function), the press coated swellable hydrophobic polymer layer (Hydroxy propyl cellulose layer (HPC), time release function) and an enteric coating layer (acid resistance function) [49].

The tablet does not release the drug in the stomach due to the acid resistance of the outer enteric coating layer. After gastric emptying, the enteric coating layer rapidly dissolves and the intestinal fluid begins to slowly erode the press coated polymer (HPC) layer. When the erosion front reaches the core tablet, rapid drug release occurs since the erosion process takes a long time as there is no drug release period (lag phase) after gastric emptying.

c) **Microbially Triggered Drug Delivery to Colon:** The micro flora count of colon is in the range of 1011 - 1012 CFU/mL [50], consisting mainly of anaerobic bacteria, e.g. Bacteroides, Bifidobacteria, Enterobacteria, Eubacteria, Clostridia, Enterococci, and Ruminococcus etc. These micro floras fulfils their energy needs by fermenting various types of the substrates that have been left undigested in the small intestine, e.g. polysaccharides, di- and tri-saccharides etc.

For this fermentation, the micro flora would produce a vast number of enzymes like glucoronidase, arabinosidase, galactosidase, xylosidase, nitroreductase, de-aminase, urea dehydroxylase and azareducatase [51].

d) The use of biodegradable polymers for colon-specific drug delivery seems to be a more site-specific approach as compared to other approaches, because of the presence of the biodegradable enzymes only in the colon. These polymers protect the drug from the environments of the stomach and small intestine and are able to deliver the drug to the colon. On reaching the colon, the polymers undergo assimilation by micro-organism or degradation by the enzyme or break down of the polymer back bone leads to a subsequent reduction in their molecular weight and thereby loss of the mechanical strength. They are then unable to hold the drug entity longer.[52]

e) **Prodrug Approach for Drug Delivery to Colon:** Prodrug is pharmacologically inactive form 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 minimize absorption and hydrolysis in the upper GI tract and undergo enzymatic hydrolysis in the colon only, there by releasing the drug moiety from the carrier. Two classes of the prodrugs are generally used. The first type of the prodrug is broken inside cells to form active substance or substances. The second type of prodrugs usually is the combination of two or more substances.

Under specific intracellular conditions, these substances react and forms active drug. Special types of prodrugs for targeted DDS have been developed during the last decades.

Targeted DDS usually includes three components:

- A drug,
- A targeting moiety,
- A carrier

The carrier binds the components of DDS together and facilitates the solubility of the whole complex. The drug (active component) is for treatment purpose. The targeting moiety/penetration enhancer increases the internalization of the active component specifically into the targeted cells enhancing specific activity of the whole DDS and reducing adverse effects on healthy tissues. Such targeted DDS should fulfil two major requirements:

- It should prevent the active component(s) from the degradation or decrease in activity during the passage to the site of action.
- It should release drug(s) from DDS inside the targeted cells.

The metabolism of azo compounds by intestinal micro flora is one of the most extensively studied bacterial metabolic processes. In 1977 it is found that the active moiety effective in the IBD was 5-amino-salicylic acid (5-ASA) and sulpha pyridine (SP) acted as a carrier only. The azo bond between these two moieties undergoes reduction in colon. A number of other linkages that are susceptible to bacterial hydrolysis specifically in the colon only have been prepared in which the drug is attached to hydrophilic moieties like amino acid, glucose, galactose, glucuronic acid, Amino acids consisting of polar groups like –NH2 and –COOH have been used as carrier for colon targeted delivery of drugs.

Limitations of the Prodrug approach are that it is not a very versatile approach as its formulation depends upon the functional group available on the drug moiety for chemical linkage. Furthermore, prodrugs are new chemical entities, and need a lot of evaluation before being used as carriers.

TABLE 5: PRODRUGS EVALUATED FOR COLON-SPECIFIC DRUG DELIVERY [54]

Drug Investigated	Carrier	Linkage hydrolysed
5- ASA(Amino salicylic acid)	Azo conjugates, Sulpha pyridine (SP)	Azo linkage
Dexamethasone/Prednisolone hydrocortisone, fludrocortisone	Saccharides carriers/Glucose/galactose/ cellobioside	Glycosidic linkage
Naloxone/Nalmefene/ Budesonide	Glucuronide conjugates glucuronic acid	Glucuronide linkage
Salicylic acid	Amino acid conjugates, glycine/Tyrosine/methionine	Amide linkage

f) **Polysaccharide Based Delivery Systems:** Use of naturally occurring polysaccharides is attracting a lot of attention for drug targeting to colon since these polymers of monosaccharide's are found in abundance, have frequent availability, are available in a variety of a structures with varied properties and are inexpensive [53]. They are easily modified chemically and biochemically and are safe, highly stable, non toxic, gel forming, hydrophilic and biodegradable. These include naturally occurring polysaccharides obtained from plant (insulin, guar gum) animal (chitosan, chondrotin sulphate) microbial (Dextran) or algal (alginates) origin. These are broken down by the colonic micro flora to simple saccharides [55]. So this fall into the category of "generally regarded as safe" (GRAS).

TABLE 6: POLYSACCHARIDES FOR COLON TARGETED DRUG DELIVERY [54]

Polymers	Chemical name	General properties	Bacterial species that degrade polysaccrides
Amylose	1, 4 D- glucose	Unbranched constituent of starch, used as tablet excipients	Bactericides, Bifidobacterium
Arabinoga lactose	1,4 and 1,3 galactose, 1,6 and 1,3 - D- arabinose and D- galactose	Natural pectin, hemi cellulose Used as a thickening agent	Bifidobacterium
Chitosan	Deacetylated -1, 4- N-acetyl –D-glucosamine	Deacetylated chitin, used as a absorption enhancing agent	Bactericides
Cylodextrin	1, 4 D- glucose	Cyclic structures of 6,7or 8 units used as a solubilising and absorption enhancing agent	Bactericides
Chondroitin sulphate	1,3 D- glucuronic acid and N- acetyl –D-glucosamine	Mucopolysacharides, contains various amounts esters of sulphate at 4 or 6 position	Bactericides
Pectin	1,4 D- galacturonic acid and 1,2 - D- rhamnose with D- galactose and D-arabinose side chain	Partial methyl ester, commonly used as thickening agent	Bifidobacterium, Eubacterium
Dextran	1, 6 D- glucose, 1,3 D- glucose	Plasma expanders	Bactericides
Guar gum	1, 6 D-galactose, 1,4 D- mannose	Galactomanan, used as a thickening agent	Bacteroides, Ruminococcus
Xylan	1,4 D- xylose with 1,3-L- arabinose side chains	Abundant hemi cellulose of Plant cell wall	Bacteroides, Bifidobacterium

2) Newly Developed Approaches for CDDS

a) **Pressure Controlled Drug-Delivery Systems:** The digestive processes within the GI tract involve contractile activity of the stomach and peristaltic movements for propulsion of intestinal contents. In the large intestine, the contents are moved from one part to the next, as from the ascending to the transverse colon by forcible peristaltic movements commonly termed as mass peristalsis [56]. These strong peristaltic waves in the colon are of short duration, occurring only three to four times a day. However, they temporarily increase the luminal pressure within the colon, which forms the basis for design of pressure-controlled systems. The luminal pressure resulting from peristaltic motion is higher in the colon compared to pressure in the small intestine, which is attributed to the difference in the viscosity of luminal contents. In the stomach and small intestine, contents are fluidic because of abundant water in digestive juices, but in the colon, the viscosity of the content is significantly increased due to reabsorption of water from the lumen and formation of faeces [57]. Takaya *et al*., (1995) have developed pressure controlled colon delivery capsules prepared using an ethyl cellulose, which is insoluble in water. In such systems drug release occurs following disintegration of water insoluble polymer capsule as a result of pressure in the lumen of the colon. The thickness of the ethyl cellulose membrane is the most important factor for disintegration of the formulation [58-59].

The system also appeared to depend on capsule size and density. Because of re absorption of water from the colon, the viscosity of luminal content is higher in the colon than in the small intestine. It has therefore, been concluded that drug dissolution in the colon could present a problem in relation to colon. Specific oral drug delivery systems. In pressure-controlled ethyl cellulose single- unit capsules, the drug is in a liquid [60]. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to human.

b) **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 [61-62]. CODESTM 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 in the colon. The system consists of a traditional tablet core containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently over coated with an enteric material, Eudragit L.

The premise of the technology is that the enteric coating protects the tablet while it is located in the stomach and then dissolves quickly following gastric emptying. The acid soluble material coating then protects the preparation as it passes through the alkaline pH of the small intestine [63]. Once the tablet arrives in the colon, the bacteria enzymatically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH surrounding the system sufficient to affect the dissolution of the acid soluble coating and subsequent drug release [64].

c) **Osmotic controlled drug delivery (OROS-CT):** The OROS-CT system can be 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 unit is bilayered laminated structure containing an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. In principle semipermeable membrane is permeable to the inward entry of water and aqueous GI fluids and is impermeable to the outward exit of the drug. An orifice is drilled into the semi permeable membrane to the drug layer.

The outside surface of the semipermeable membrane is then coated by eudragit®S100 to 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 result water enters the unit causing the osmotic push compartment to swell forcing the drug out of the orifice into colon. For treating ulcerative colitis, each push pull unit is designed with a 3-4 hour post gastric delay to prevent drug delivery in the small intestine. Drug release begins when the unit reaches the colon. OROS-CT units can maintain a constant release rate for up to 24 h in the co

d) **PULSINCAP System:** Pulsincap was developed by R.R.Scherer International Corporation, Michigan, US. This system consists of water insoluble capsule enclosing the drug reservoir. To seal the drug contents in the capsule body a swellable hydrogel plug was used.[66]When this capsule came 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.

e) Polymers used for designing the hydrogel plug are various viscosity grades of hydroxyl propyl methyl cellulose, polymethyl methacrylates, poly vinyl acetate and poly ethylene oxide. The length of the plug and its point of insertion into the capsule controlled the lag time. Pulsincap was studied in human volunteers and was reported to be well tolerated [67-69].

As the swelling hydrogel polymer plug replaced the erodible tablet, the dependence of the dimensional accuracy between the plug and the capsule for the pulling mechanism of the plug from the capsule was also overcome. Ross et al used low substituted hydroxyl propyl cellulose for the expulsion system for the release of

propanolol over a time period of 2-10 hr. This could be controlled using compressed erodible tablets made of lactose and HPMC [70]. Kroger and Bodmeier [71] studied the release of Chlorphenir-amine utilizing the erodible plugs.

f) **PORT system:** The Port system was developed by Therapeutic System Research Laboratory Arm Arbor, Michigan, USA. This system comprises of capsule coated with semipermeable membrane. Inside the capsule there is an insoluble plug consisting of osmotically active agents and the drug formulation [72]. When in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after a lag time. The lag time is controlled by coating thickness. The system showed good correlation in lag times of in-vitro and in-vivo experiments in humans. It used to deliver methylphenidate to school age children for the treatment of attention deficit hyper activity disorder (ADHD) [73-74].

g) **Time clock system:** A delivery system called Time Clock has been exploited to release the drug in the colon [75]. It is composed of a solid dosage form coated with a hydrophobic surfactant layer to which a water-soluble polymer is added to improve adhesion to the core. The outer layer redisperses in the aqueous environment in a time proportional to the thickness of the film and the core is then available for dispersion. In a study with human volunteers, it was shown that the lag time was independent of gastric residence time and hydrophobic film redispersing did not appear to be influenced by the presence of intestinal digestive enzymes or by mechanical action of the stomach [76].

h) **Chronotropic system:** In this system drug reservoir is surrounded with a soluble barrier layer which dissolve with time and drug release at once after this lag time. These systems are based upon a drug reservoir surrounded with a soluble barrier layer that dissolves with time and the drug releases at once after this lag time. Chronotropic system consists of a core containing reservoir coated by a hydrophilic polymer HPMC [77-79]. To overcome intra subject variability in gastric emptying rates an additional enteric coated film is given outside the layer. An additional enteric-coated film is given outside this layer to overcome intra subject variability in gastric emptying rates. The lag time and the onset of action are controlled by the thickness and the viscosity grade of HPMC [80].

Limitations and challenges in Colon Targeted Drug Delivery:

- One of the challenges in the development of the colon-specific drug delivery systems is to establish an appropriate dissolution testing method for evaluation of the designed system *in-vitro*. This is due to a rationale after the colon specific drug delivery system is quite diverse.

- As a site for the drug delivery, the colon offers a near neutral pH, a long transit time, reduced digestive enzymatic activity and increased responsiveness to the absorption enhancers; however, targeting of drugs to the colon is very complicated. Due to its location in the distal part of the alimentary canal, the colon is difficult to access. In addition, the wide range of pH values and different enzymes present throughout the gastrointestinal tract, through which the dosage form has to travel before reaching the target site, further complicate the reliability and delivery efficiency.

- Successful delivery through this site requires the drug to be in the solution form before it arrives in colon or, alternatively, it much less and it is more viscous than in the upper part of GI tract.

- In addition, the stability of the drug must be taken into consideration while designing the delivery system. The drug may potentially bind in a nonspecific way to dietary residues, mucus, intestinal secretions or faecal matter.

- The resident microflora affects the colonic performance via metabolic degradation of the drug. Lower surface area and relative “tightness” of the tight junctions in colon can restrict the drug transport across the mucosa and into the systemic circulation. [54]

Opportunities in Colon Targeted Drug Delivery:

- Targeted delivery to the colon is being explored not only for the local colonic pathologies, thus avoiding the systemic effects of drugs or inconvenient and painful trans colonic administration of drugs, but can be used for systemic delivery of drugs like proteins and peptides, which are otherwise degraded and/or poorly absorbed in stomach and small intestine but can be better absorbed from the colon.

- This is also a potential site for treatment of diseases which are sensitive to circadian rhythms such as asthma, arthritis and angina. Moreover, if there is an urgent need for the delivery of drugs to the colon that is absorbable in the colon, such as steroids, which would increase the efficiency and enable reduce the required effective dose.

- The treatment of disorders of the large intestine, such as irritable bowel syndrome (IBS), Crohn's disease ,colitis, and other colon diseases, where it is necessary to attain a high concentration of the drug, may be efficiently achieved by the colon-specific delivery.

- The development of a dosage form that improves the oral absorption of the peptide and protein drugs whose bioavailability is very low because of the instability in the GI tract is one of the greatest challenges for the oral peptide delivery.

- More research is focused on particular the specificity of drug uptake at the colon site is necessary. These studies would significant in advancing the cause of the colon targeted drug delivery in future [81].

CONCLUSION: Site for drug delivery and absorption increasingly become important for colonic region of GIT. In the terms of both local and systemic treatment CDDS offers considerable benefits to patients. Although various approaches were proposed for colon target drug delivery: Prodrugs, pH, time dependent systems and microbially triggered drug delivery system. Of these, first three approaches are not ideal for CDDS. Novel approaches developed for CDDS are more specific.

Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. Considering the sophistication of colon-specific drug delivery systems, and the uncertainty of current dissolution methods in establishing possible *in-vitro/in-vivo* correlation, challenges remain for pharmaceutical scientists to develop and validate a dissolution method that incorporates the physiological features of the colon, and yet can be used routinely in an industry setting for the evaluation of CDDS.

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