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Review Article

NOVEL COLON SPECIFIC DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

The review focus on the potential opportunities and challenges available in new area of colon targeted drug delivery system. The colon is a site where both local and systemic delivery of drugs can take place. Colon was considered as "BLACK BOX" as, most of drugs are absorbed from upper part of GIT tract. Lack of digestive enzymes and long transit time, has been provided to design colon specific drug delivery system. Present topic into the utilization of the metabolic activity and the colonic environment in the lower gastrointestinal tract has attained immense value in the design of novel colon targeted drug delivery systems by the utilization of natural biodegradable polymers. It is more effective to treat colonic diseases such as ulcerative colitis, colorectal cancer, and Crohn's disease with direct delivery of drugs to the affected area. Newly developed colon specific drug delivery system (CDDS), which includes pressure controlled colonic delivery capsules (PCDCS), CODES and osmotic controlled drug delivery are unique in terms of achieving in vivo site specificity and feasibility of manufacturing process. This review also focuses on evaluations of CDDS in general.

Keywords: Colon specific drug delivery, Pulsatile drug delivery, Novel approaches, Evaluation.

INTRODUCTION

By definition, colonic delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e. colon). Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs. The colon specific drug delivery system (CDDS) 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 the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon.[1, 2] The site-specific delivery of drugs to lower parts of the GI tract is advantageous for localized treatment of several colonic diseases, mainly inflammatory bowel disease. Other potential applications of colonic delivery include chronotherapy, prophylaxis of colon cancer and treatment of nicotine addiction[3, 4]. It has also gained increased importance not just for the delivery of drugs for the treatment of local diseases, but also potential site for the systemic delivery of therapeutic proteins and peptides which are being delivered by injections. These delivery systems when taken orally, allow drugs to release the drug from the delivery system once the delivery system arrives into the colon[5, 6].

These delayed mechanisms are designed to improve the efficacy of the drug by concentrating the drug molecules where they are need most, and also minimize the potential side effects and drug instability issues associated with premature release of drug in the upper parts of the GIT, namely stomach and small intestine.

Colon targeted drug delivery would ensures direct treatment at the disease site, lower dosing and less systemic side effects. In addition to restricted therapy, the colon can also be utilized as a portal for the entry of drugs into the systemic circulation. For example, molecules that are degraded/poorly absorbed in the upper gut, such as peptides and proteins, may be better absorbed from the more benign environment of the colon. . Overall, there is less free fluid in the colon than in the small intestine and hence, dissolution could be problematic for poorly water-soluble drugs. In such instances, the drug may need to be delivered in a presolubilized form, or delivery should be directed to the proximal colon, as a fluid gradient exists in the colon with more free water present in the proximal colon than in the distal colon. Aside from drug solubility, the stability of the drug in the colonic environment is a further factor that warrants attention. The drug could bind in a nonspecific manner to dietary residues, intestinal secretions, mucus or general faecal matter, thereby reducing the concentration of free drug. Moreover, the resident micro-flora could also affect colonic performance via degradation of the drug[7].

Advantages of CDDS

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.[10] 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.

Why is colon targeted drug delivery needed?

- Colon-specific drug delivery system is considered to be beneficial in the treatment of colon diseases.
- Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects.
- Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery.
- The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine (targeted).
- A number of others 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.

The colon

The entire colon is divided into five major segments across its 150 cm length. The last anatomic segment before the anus is the rectum. Peritoneal folds called mesentery supports ascending and descending colon. The right colon consists of the cecum, ascending colon, hepatic flexure and the right half of the transverse colon. The left colon consists of the left half of the transverse colon, splenic flexure, descending colon, and sigmoid. (Figure 1)

Physiology of the colon[8]

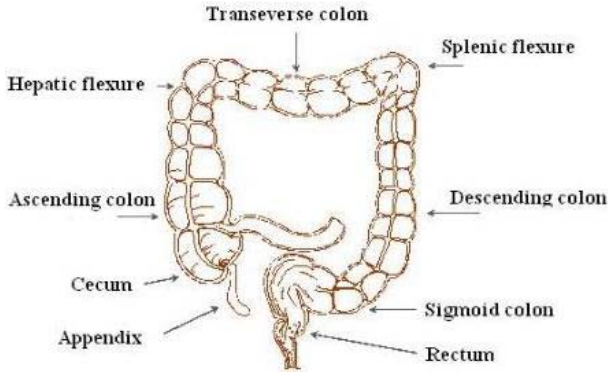

Fig. 1: Anatomy of colon

The main functions of the colon are elimination of waste material, storage of faeces and reabsorption of water and electrolytes. The storage function of the colon is the main function of the colon that allows a longer period for absorption of useful material by preventing rapid elimination of colonic contents. All colonic area are capable of storing function but with different storage capacity. The ascending colon is thought to be the main storage site [10].It was shown that only 150 ml of water is eliminated with faeces from each 1000 ml of chyme in the colon[9]. The slower movement in the colon compared with any other area of the G.I.T allows for this absorption. Water reabsorption in the colon occurs as a result of the absorption of sodium and chloride ions and associated excretion of potassium and bicarbonate ions [12]. The first portion, including the cecum, ascending colon, and part of the transverse colon, has a unique pattern of motility compared to the subsequent sections. This area has a motility that was first described by Cannon[12], (1902) as antiprestaltic. Antiprestalsis causes the chyme to be pushed back towards the ileocecal junction this results in thorough mixing and increased efficiency of absorption of water and electrolytes from the chyme[13]. Antiprestalsis leads to a prolonged residence time in the proximal colon. This effect, together with the fact that the contents are less viscous at this site[14], makes the ascending colon an ideal site for drug release.

Table 1: Colon targeting diseases, drugs and sites

Target sites	Disease conditions	Drug and active agents
Topical action	Inflammatory Bowel Diseases, Irritable bowel disease and Crohn's disease. Chronic pancreatitis	Hydrocortisone, Budenoside, 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 Oral delivery of peptides	Steroids Insulin
	Oral delivery of vaccines	Typhoid

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: More consistent ranging (3-4 hr) and rich in digestive enzymes such as esterase, lipase, amylase, protease and glycosidase.

Table 2: Gastrointestinal Transit time of contents

Organ	Transit Time (hr)
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: [15]

- 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 (103-104CFU/ml)
- Colon (1011-1012CFU/ml) 400 species and most of them are anaerobes and bacteroids.

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 [16].

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 [17], 5-fluorouracil, cephradine, riboflavin, L-carnitine[18], theophylline[19], naproxen[20], oxprenolol[21], nifedipine[22] and indomethacin [23].

Strategies of colon drug delivery system

Localizing orally administered drugs in the colon is particularly complicated because the colon located at the end of the alimentary canal which makes it difficult to access. Several methods of colonic targeting have been proposed. These include taking advantage of the utilization of pH changes within the G.I.T, the apparent consistency of small intestinal transit times, and the exploitation of bacterial enzymes localized in the colonic region of the G.I.T.

Utilization of pH changes through G.I.T.

Colon drug delivery can be approached by using polymers that only dissolve at certain pH values, such as cellulose acetate phthalate (CAP), shellac and acrylic acid resins (Eudragits). Most pH dependent polymers contain carboxyl groups making them insoluble at low pH values and soluble at higher pH values. The number of carboxyl groups in polymer molecule determine its threshold pH (the specific pH at which the polymer molecule dissolve). Most of these polymers are used as enteric coating. Number of Eudragit polymers S or L or combinations have been investigated for colonic delivery system [24, 25].

Utilization of transit time

Rather than relying on the colonic pH to trigger dissolution and then tablet disintegration, some research has considered the possibility of utilization of the fact that within the G.I.T, the transit time from leaving the stomach to arriving at the I.C.J is the most reproducible of the various transit times. Pulsincap and Oros CT are considered important examples using this approach [26,27].

Utilization of the large intestine microflora

The abundant metabolic activity of microflora present in the large intestine can be exploited in selectively targeting drug release in the colon. Among of multitude of bacterial enzymes that are produced in the colon, two main classes are, on the whole, thought to be reproducible enough and present in the sufficient quantity to be exploited in drug targeting. These are azoreductases, enzymes that reduce azo-bond, and the polysaccharides, that is the large number of mainly glycosidic enzymes which degrade the polysaccharides present in the colon.

Prodrug concept

A successful prodrug colonic delivery is the one that passes intact and unabsorbed from the upper GIT and undergo biotransformation in the colon releasing the active drug molecule. Amino-acid, glycoside, glucouronide, azo, dextran, and cyclodextrin conjugates are some of the conjugates evaluated for colon-specific delivery. Generally, a prodrug is successful as a colon drug carrier if it is hydrophilic and bulky to minimize absorption from the upper G.I.T., and if once in the colon, it is converted into a more lipophilic drug molecule, which is then available for absorption. Harboe et al.[28] (1988a; b; 1989) showed the potential of dextran prodrugs for colon specific delivery of naproxen and any drug containing a carboxylic acid function.

Approaches to Colonic Drug Delivery through Oral Route

Oral route generally preferred by the patient than the rectal route. Colon is the most distal segment of g.i.t. that's why orally administered drug must retard drug release in the upper g.i.t. but must release promptly on entry into the distal colonic part. In colon due to presence of low fluid volume & viscous nature of luminal content, the drug dissolution & release from the formulation may vary. Colonic microflora also shows impact on the stability of released drug. Inspite of these difficulties various approaches & systems have been developed to target the drug to the colon.

1. pH dependent delivery

In g.i.t. there is presence of pH gradient which approximately ranges from 1.2 in stomach, 6.6 in proximal small intestine, 7.5 in distal intestine & pH of colon is about 6.4. Generally Eudragit S is used for the colon delivery it dissolves at pH greater than 7.0, which results in premature drug release from the system. It is concluded that pH of g.i.t. was not a reliable criteria for colonic targeting. [29] Problem of premature drug release can be overcomed by the use of Eudragit FS. [30]

2. Pressure dependent delivery

The pressure controlled colon delivery capsule utilizes the increase in pressure of the luminal contents of the colon. Increase in luminal pressure is due to reabsorption of water in this region. The drug is dispersed in suppository base & coated with ethyl cellulose for the preparation of such system. Temperature of body is responsible for suppository base to melt & increases the volume which forms balloon of ethyl cellulose and filled with liquid. This balloon can withstand with the contraction of small intestine (peristalsis) but ruptures when subjected to intensive contraction in the colon & contents of thicker viscosity. This system is used for the production of single unit system. [31]

3. Bacteria dependent delivery

In these systems colonic bacteria are utilized to degrade the substrate. The bacterial amount has been estimated about 10^{11} per gram in the colon & having around 400 species (anaerobic in nature). Earlier polymer cross linked with azo aeromatic groups was used but due to potential carcinogenic activity now a days natural polysaccharides are used. Natural polysaccharides generally undergo premature drug release so they are chemically modified or mixed with hydrophobic polymers. This polymer shows good film forming properties, resistant to pancreatic enzymes but they will undergo degradation due to bacterial enzyme. [32]

4. Time dependent delivery (Pulsatile drug delivery)

Pulsatile release systems are formulated to undergo a lag-time of predetermined span of time of no release, followed by a rapid & complete release loaded drugs(s). The approach is based on the principle of delaying the time of drug release until the system transits from mouth to colon. A lag-time of 5 hours is usually considered sufficient since small intestine transit is about 3-4 hours, which is relatively constant and hardly affected by the nature of formulation administered. This system offers many advantages over conventional oral drug delivery systems like patient compliance, reduced dosage, reduced dosage frequency, avoidance of side effects, avoidance of peak & valley fluctuation, nearly constant drug level at the target site. [33]

New approaches for colon-specific drug delivery

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

A) Pharmaceutical formulation using biodegradable polysaccharides and hydrogels

This approach is based on the inability of stomach and small intestine enzymes in humans to digest certain plant polysaccharides such as pectin, guar gum, amylose, chondroitin, chitosan etc. The incorporation of a drug into a pharmaceutical formulation using such polysaccharide hydrogels either by coating, embedding in a polymer matrix, or any other method has considerable advantages over the prodrug approach. First, no chemical modification of the drug is required. This is extremely important, as the drug in a new dosage form will not considered a new chemical entity. Formulation also circumvents the need for specific functional groups on the drug, which is vital in prodrug synthesis.

a) Hydrogels

The hydrogels contain acidic co-monomers and enzymatically degradable azoaromatic crosslinks. In the acidic pH of stomach, the Gels have a low degree of swelling, which protect the drug against degradation by digestive enzymes. As the gels pass down the GI tract, the degree of swelling increases. On entering the colon, the gels reach a degree of swelling making the cross-links accessible to enzymes (azoreductases) or mediators (electron carriers). A number of drug delivery devices have been proposed to deliver the drug for efficient therapy. Among them, hydrogels, specially based on polysaccharides, have attracted considerable

attention as an excellent candidate for controlled release devices or targetable devices of the therapeutic agents. The release rate of drugs from hydrogels was primarily determined by the swelling extent, which further enhanced by addition of enzyme in the buffer solutions whereas swelling of polymeric networks was depended on composition of copolymer and pH of the surrounding medium. The controlled releases of active anti-microbial agents- amoxicillin, metronidazole, oxytetracycline and tetracycline HCl from the polymeric matrix have been well reported.

The release of water-soluble drugs, entrapped in a hydrogels, occur only after water penetrates the polymeric networks to swell and dissolve the drug, followed by diffusion along the aqueous pathways to the surface of the device. The release of drug is closely related to the swelling characteristics of the hydrogels, which in turn, is a, key function of chemical architecture of the hydrogels. In the present study the effect of pH on the release pattern of tetracycline have been studied by varying the pH of the release medium. The amount of drug release in pH7.4 buffer was higher than the release medium of pH2.2 buffer and distilled water. The swelling of hydrogels, increased when the pH of the medium changed from acidic to basic. At lower pH values the -CONH2 groups does not ionized and keep the polymeric networks at its collapsed state. At high pH values, it is partially ionized, and the charged – COO groups repel each other, leading to the higher swelling of the polymer and resultant to more drug release. The release of drug was observed to be faster in pH 7.4 (Equation 1).

From the percent cumulative release studies of tetracycline it was observed that first 50% of the total release occurred in 90min., 120min. and 135min. in releasing medium of pH7.4 buffer, pH2.2 buffer and distilled water respectively. The diffusion exponent 'n' have 0.74, 0.60 and 0.56 values and gel characteristic constant 'k' have 1.272×10-2, 2.754×10-2 and 3.639×10-2 values in distilled water, pH2.2 buffer and pH7.4 buffer respectively for the tetracycline release from the hydrogels and these values were obtained from the slope and intercept of the plot between ln Mt/M8 versus ln t (Equation 2). It means Non-Fickian or Anomalous diffusion occurs for the tetracycline release from the hydrogels. It is also observed that in each release medium the initial diffusion coefficient was observed to more than late time diffusion coefficient.

Diffusion mechanism of the drugs from the polymeric matrix can be calculated from the

Equation;

$$\frac{M_t}{M_\infty} = k t^n \longrightarrow (1)$$

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi \lambda^2}\right)^{0.5} \longrightarrow (2)$$

$$D_A = \frac{0.049\ \lambda^2}{t^{1/2}} \longrightarrow (3)$$

$$\frac{M_t}{M_\infty} = 1 - \left(\frac{8}{\pi^2}\right) \exp\left[\frac{(-\pi^2 Dt)}{\lambda^2}\right] \longrightarrow (4)$$

Where; Mt / M8 is the fractional release of drug in time t, 'k' is the constant characteristic of the drug polymer system, and 'n' is the diffusion exponent 'D' is the diffusion coefficient and 'λ' is the thickness of the sample.

b) Chitosan

Some of biodegradable polysaccharides are used for colon drug delivery system; Table (3) is showing examples of them. One of the most famous polysaccharide is chitosan, which has universal using. It is a linear polysaccharide composed of randomly distributed ß-(1-4)-linked D glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit). It has a number of commercial and possible biomedical uses.

Table 3: Different biodegradable polysaccharides used for colon drug delivery system

Polysaccharide	General properties	Bacterial species that degrade polysaccharide
Amylose	Unbranched, constituents of starch, used as excipient in tablet formation.	Bacteroids, Bifidobacterium
Arabinogalactan	Natural Pectin ,hemicellulose, used as thickening agent	Bifidobacterium
Chitosan	Deacetylated chitin, used as absorption enhancement agent	Bifidobacterium
Chondroitin sulphate	Mucopolysaccharide containing various amounts of sulphate ester groups at the 4- or 6- position	Bacteroids
Dextran	Plasma expanders	Bacteroids
Guar gum	Galactomannan, used as thickening agent	Bacteroids, Ruminococccus
Pectin	Partial methyl ester, commonly used as thickening agent.	Bacteroids Bifidobacterium, Eubacterium
Xylan	Abundant hemi cellulose of plant cell walls	Bacteroids, Bifidobacterium

Chitosan is produced commercially by deacetylation of chitin, which is the structural element in the exoskeleton of crustaceans (crabs, shrimp, etc.). The amino group in chitosan has a pKa value of 6.5, thus, chitosan is positively charged and soluble in acidic to neutral solution with a charge density dependent on pH and the degree of acetylation % (DA-value). In other words, chitosan is bioadhesive and readily binds to negatively charged surfaces such as mucosal membranes. Chitosan enhances the transport of polar drugs across epithelial surfaces, and is biocompatible and biodegradable. Purified qualities of chitosans are available for biomedical applications.

Chitosan was used in oral drug formulations to provide sustained release of drugs. Recently, it was found that chitosan is degraded by the microflora that is available in the colon. As a result, this compound could be promising for colon-specific drug delivery.

Chitosan was reacted separately with succinic and phthalic anhydrides. The resulting semisynthetic polymers were proved for colon-specific, orally administered drug delivery systems. Systems for colon delivery containing acetaminophen (paracetamol), mesalazine (5-ASA), sodium diclofenac, and insulin have been studied and showed satisfactory results [34].

c) Eudragits

Methacrylic acid copolymers are the frequently used pH-dependent coating polymers, they are known commercially as Eudragit (which is a registered trademark of Rohm Pharmaceuticals, Darmstadt, Germany). Eudragit® L and Eudragit S are used in combination for meeting the effective pH-dependent coating. Eudragit L100 and S 100 are copolymers of methacrylic acid and methyl methacrylate in different ratios of carboxyl to ester groups which is about approximately 1:2 in Eudragit® S 100 and 1:1 in Eudragit®L100. These polymers after forming salts dissolve above pH 5.5 and disperse in water forming latex. Eudragit® L30D-55 is a ready to use aqueous dispersion of Eudragit ® L100-55. The solubility of the Eudragit S in water depends on the ratio of free carboxyl groups to the esterified groups. The factor, which is critical, is that influences the performance of these polymers, is the pH value at which dissolution happens. Polymers with an ionizable phthalic acid group dissolve much faster and at a lower pH than those with acrylic or methacrylic acid groups.

The permutation of Eudragit® L100-55 and Eudragit S100 could be effectively used from aqueous system to coat tablets for colon targeted drug delivery of drugs and can be adjusted to deliver drug at any other desirable site of the intestinal region of the GIT on the basis of pH unevenness.

Various Eudragit coated oral dosage forms of Salsalazine are presently in use for the treatment of ulcerative colitis and Crohn's disease. Morishita et al., [35] 1993, compared the insulin delivery of two formulations containing Eudragit® L-100 and Eudragit ®LS respectively. Formulation containing Eudragit S showed optimal delivery of insulin in the ileum at pH 7.

d) Sodium alginate

Sodium alginate is simply the sodium salt of alginic acid, with an empirical chemical formula NaCHO. It is found as a gum, when extracted from the cell walls of brown algae and appears to be resistant to digestion by digestive enzymes. Sodium alginate is fermented, in part, by colonic bacteria to the short chain fatty acids acetate, propionate, and butyrate [36].

Sodium alginate can be used for targeting colonic and gastric mucosa by preparing floating beads as well as other specific organs by preparation of nanoparticles based on alginate. Alginate beads are reported to float on a dissolution medium, and the porosity can be directed by method of drying.

Recent method shows that gelatin capsules when coated with various concentrations of sodium alginate and cross-linked with suitable concentrations of calcium chloride and checked in vitro for resistance to gastric and intestinal medium. Gelatin capsules when coated with 20% w/v of the polymer were assessed in human volunteers for in vivo gastro-intestinal tract behaviour. The uncoated gelatin capsules disintegrated in the stomach within 15 min of ingestion, after radiographical studies. But the alginate coated gelatin capsules remained intact as long as they were maintained in the stomach (up to 3 h) and then travelled to the ileocecal region of the intestine and disintegrated [37].

B) Newly Developed Approaches for CDDS

a. Pressure Controlled Drug-Delivery Systems

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. Takaya et al. developed pressure controlled colon-delivery capsules prepared using ethylcellulose, which is insoluble in water[38].In such systems, drug release occurs following the disintegration of a water-insoluble polymer capsule because of pressure in the lumen of the colon. The thickness of the ethylcellulose membrane is the most important factor for the disintegration of the formulation[39, 40]. The system also appeared to depend on capsule size and density. Because of reabsorption of water from the colon, the viscosity of luminal content is higher in the colon than in the small intestine. It has therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems. In pressure controlled ethylcellulose single unit capsules the drug is in a liquid.[41] Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to humans.

b. Novel Colon Targeted Delivery System (CODESTM)

CODESTM is an unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems.[42,43] 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, (Fig. 2). The system consists of a traditional tablet core containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently overcoated 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[44].Once the tablet arrives in the colon, the bacteria enzymetically 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.

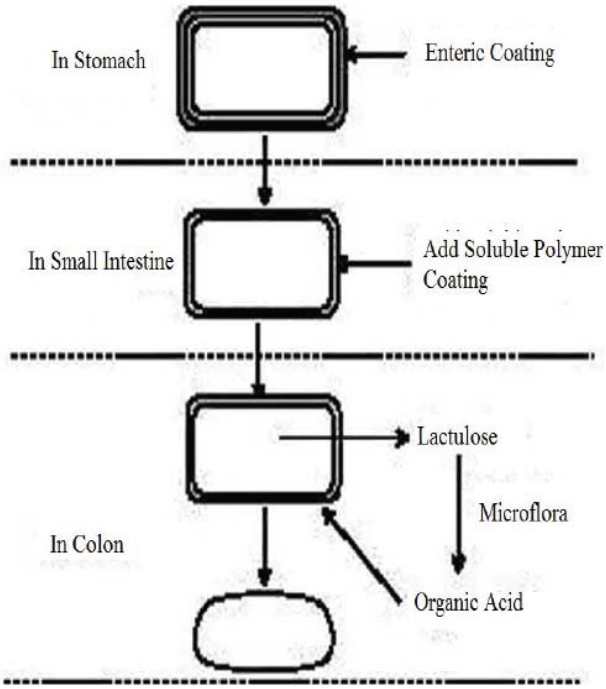

Fig. 2: Schematics of the conceptual design of CODES

c. Osmotic Controlled Drug Delivery (ORDS-CT)

The OROS-CT (Alza corporation) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable.[45] The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule, (Fig. 3).[46] Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. An orifice is drilled through the membrane next to the drug layer. Immediately after the OROS-CT is swallowed, the gelatin capsule containing the push-pull units dissolves. Because of its drug-impermeable enteric coating, each push-pull unit is prevented from absorbing water in the acidic aqueous environment of the stomach, and hence no drug is delivered. As the unit enters the small intestine, the coating dissolves in this higher pH environment (pH >7), water enters the unit, causing the osmotic push compartment to swell, and concomitantly creates a flowable gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semipermeable membrane.

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 begins when the unit reaches the colon. OROS-CT units can maintain a constant release rate for up to 24 hours in the colon or can deliver drug over a period as short as four hours. Recently, new phase transited systems have come which promise to be a good tool for targeting drugs to the colon[47]. Various in vitro / in vivo evaluation techniques have been developed and proposed to test the performance and stability of CDDS.

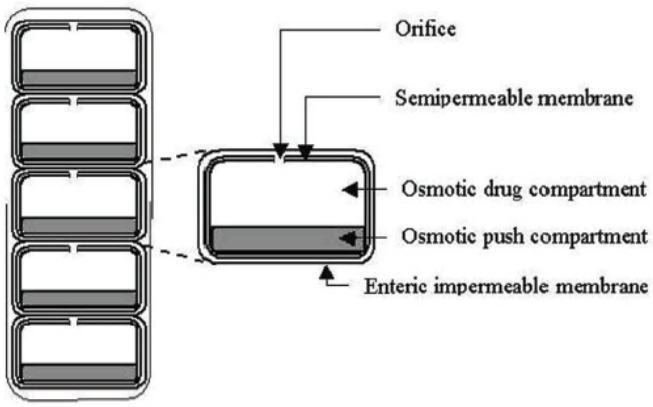

Fig. 3: Cross-Section of the OROS-CT colon targeted drug

For in vitro evaluation, not any standardized evaluation technique is available for evaluation of CDDS because an ideal in vitro model should posses the in-vivo conditions of GIT such as pH, volume, stirring, bacteria, enzymes, enzyme activity, and other components of food. Generally, these conditions are influenced by the diet,

physical stress, and these factors make it difficult to design a slandered in-vitro model. In vitro models used for CDDS are

i) In vitro dissolution test

Dissolution of controlled-release formulations used for colon-specific drug delivery are usually complex, and the dissolution methods described in the USP cannot fully mimic in vivo conditions such as those relating to pH, bacterial environment and mixing forces.[22]Dissolution tests relating to CDDS may be carried out using the conventional basket method. Parallel dissolution studies in different buffers may be undertaken to characterize the behavior of formulations at different pH levels. Dissolution tests of a colon-specific formulation in various media simulating pH conditions and times likely to be encountered at various locations in the gastrointestinal tract have been studied [48]. The media chosen were, for example, pH 1.2 to simulate gastric fluid, pH 6.8 to simulate the jejunal region of the small intestine, and pH 7.2 to simulate the ileum segment. Enteric-coated capsules for CDDS have been investigated in a gradient dissolution study in three buffers. The capsules were tested for two hours at pH 1.2, then one hour at pH 6.8, and finally at pH 7.4.[49]

ii) In vitro enzymatic tests

Incubate carrier drug system in fermenter containing suitable medium for bacteria (strectococcus faccium and B. Ovatus). The amount of drug released at different time intervals are determined. Drug release study is done in buffer medium containing enzymes (ezypectinase, dextranase), or rat or guinea pig or rabbit cecal contents. The amount of drug released in a particular time is determined, which is directly proportional to the rate of degradation of polymer carrier.

iii) In vivo evaluation

A number of animals such as dogs, guinea pigs, rats, and pigs are used to evaluate the delivery of drug to colon because they resemble the anatomic and physiological conditions as well as the microflora of human GIT. While choosing a model for testing a CDDS, relative model for the colonic diseases should also be considered. Guinea pigs are commonly used for experimental IBD model. The distribution of azoreductase and glucouronidase activity in the GIT of rat and rabbit is fairly comparable to that in the human [50]. For rapid evaluation of CDDS, a novel model has been proposed. In this model, the human fetal bowel is transplanted into a subcutaneous tullel on the back of thymic nude mice, which bascularizes within four weeks, matures, and becomes capable of developing of mucosal immune system from the host.

Drug Delivery Index (DDI) and Clinical Evaluation of Colon-Specific Drug Delivery Systems

DDI is a calculated pharmacokinetic parameter, following single or multiple dose of oral colonic prodrugs. DDI is the relative ratio of RCE (Relative colonic tissue exposure to the drug) to RSC (Relative amount of drug in blood i.e. that is relative systemic exposal to the drug). High drug DDI value indicates better colon drug delivery. Absorption of drugs from the colon is monitored by colonoscopy and intubation. Currently, gamma scintigraphy and high frequency capsules are the most preferred techniques employed to evaluate colon drug delivery systems.

Limitations and challenges in colon targeted drug delivery

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

2. As a site for drug delivery, the colon offers a near neutral pH, reduced digestive enzymatic activity, a long transit time and increased responsiveness to absorption enhancers; however, the targeting of drugs to the colon is very complicated. Due to its location in the distal part of the alimentary canal, the colon is particularly difficult to access. In addition to that 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.

3. Successful delivery through this site also requires the drug to be in solution form before it arrives in the colon or, alternatively, it should dissolve in the luminal fluids of the colon, but this can be a limiting factor for poorly soluble drugs as the fluid content in the colon is much lower and it is more viscous than in the upper part of the GI tract.

4. In addition, the stability of the drug is also a concern and must be taken into consideration while designing the delivery system. The drug may potentially bind in an on specific way to dietary residues, intestinal secretions, mucus or faecal matter.

5. The resident microflora could also affect colonic performance via metabolic degradation of the drug. Lower surface area and relative 'tightness' of the tight junctions in the colon can also restrict drug transport across the mucosa and into the systemic circulation. The literature also suggested that the cytochrome P-450(3A) class of drug metabolizing enzymes have lower activity in the colonic mucosa. A longer residence time of 3 to 5 days results in elevated plasma levels of the drugs and therefore higher bioavailability in general, but especially for drugs that are substrates for this class of enzyme.

Opportunities in colon targeted drug delivery

- In the area of targeted delivery, the colonic region of the GI tract is the one that has been embraced by scientists and is being extensively investigated over the past two decades.
- Targeted delivery to the colon is being explored not only for local colonic pathologies, thus avoiding systemic effects of drugs or inconvenient and painful transcolonic administration of drugs, but also for systemic delivery of drugs like proteins and peptides, which are otherwise degraded and/or poorly absorbed in the stomach and small intestine but may be better absorbed from the more benign environment of the colon.
- This is also a potential site for the treatment of diseases sensitive to circadian rhythms such as asthma, angina and arthritis. Moreover, there is an urgent need for delivery of drugs to the colon that reported to be absorbable in the colon, such as steroids, which would increase efficiency and enable reduction of the required effective dose.
- The treatment of disorders of the large intestine, such as irritable bowel syndrome (IBS), colitis, Crohn's disease and other colon diseases, where it is necessary to attain a high concentration of the active agent, may be efficiently achieved by colon-specific delivery. The development of a dosage form that improves the oral absorption of peptide and protein drugs whose bioavailability is very low because of instability in the GI tract is one of the greatest challenges for oral peptide delivery.
- The bioavailability of protein drugs delivered at the colon site needs to be addressed. More research is focused on the specificity of drug uptake at the colon site is necessary. Such studies would significant in advancing the cause of colon targeted drug delivery in future.

REFERENCES

1. Philip AK, Dabas S, Pathak K. Optimized prodrug approach: A means for achieving enhanced anti-inflammatory potential in experimentally induced colitis. J Drug Target 2009; 17:235-241.
2. Oluwatoyin AO, John TF. In vitro evaluation of khaya and albizia gums as compression coating for drug targeting to the colon. J Pharm Pharmacol 2005; 57: 63-168.
3. Abdul B, John B. Perspectives on Colonic Drug Delivery, Business Briefing, Pharmatech, 2003, 185–190.

4. Bajpai S K, Bajpai M, Dengree R. Chemically treated gelatin capsules for colontargeted drug delivery: a novel approach, J. Appl. Polym.Sci., 2003, 89, 2277–2282.
5. M.Najmuddin, Vishal Patel, Aejaz Ahmed, Shelar and T. Khan. Preparation and evaluation of flurbiprofen for colonic drug delivery system. IJPPS 2010; 2 (2).
6. Ranamazumder, Lila K Nath, Anwarul Haque, Taras Ankar Malty, K. Prasanta. Formulation and invitro evaluation of natural polymers based on microspheres for colonic drug delivery system. IJPPS 2010; 2 (2).
7. Chourasia M K, Jain S K. Pharmaceutical Approaches to Colon Targeted Drug Delivery, Journal of pharmaceutical sciences 2003; 6(1): 33-66.
8. Sarasija S, Hota A. Colon-specific drug delivery systems, Indian journal of pharmaceutical sciences 2000; 62(1): 1- 8.
9. Philip AK, Dubey RK, Pathak K. Optimizing delivery of flurbiprofen to the colon using a targeted prodrug approach. J Pharm Pharmacol 2008; 60:607- 613
10. Christensen, J., The response of the colon to eating. Am. J. Clin. 1985; Nutr.42: 1025-1032.
11. Rangachari, P.K. Six-pack balancing act: a conceptual model for the intestinal lining. Can. J. Gastroenterol. 1990; 4: 201-208.
12. Dawson, D.C., (1991). Lon channels and colonic salt transport. Annu. Rev. Physiol., 53, 321-329.
13. Cannon, W.B., (). The movements of the intestines studied by means of rontgen rays. Am.J.Physiol. 1902; 6: 251.
14. Christensen, J., (1981). Motility of the colon, in Physiology of the gastro intestinal tract, 1st ed., Vol 1, Jonson-LR, Ed, Raven Press, New York.
15. Evans, D.F; Pye, G.; Bramley, R.; Clark, A. G.; Dyson, T. J.; Hardcastle, J. D., (1988). Measurement of gastrointestinal PH profiles in normal ambulantant human subjects. Gut, 29; 1035-1041.
16. Sarasija S., Hota A., Colon-specific drug delivery systems, Indian J Pharm Sci. 2000; 62 (1): 1-8
17. Shiga, M., Hayashi, M., Horie, T., Awazu, S., (1987). Differnces in the promotion mechanism of the colon absorption of antipyrine, phenol red and cefmetazole. J.Pharm. Pharmacol. 39: 118-123.
18. Leo, A., Hansch, C., Elkins, D., (1971). Partition coefficients and their uses. Chem. Rev., 71: 525–616.
19. Staib, A., H., Loew, D., Harder, S., Graul, E.H., Pfab., Measurement of theophylline absorption from different regions of the gastrointestinal tract using a remote controlled drug delivery device. Eur. J. Pharmacol. 1986; 30: 691-697.
20. Harboe, E., Larsen, C., Johansen, M., Olesen, H.P., Macromolecular prodrugs. XV. Colon-targeted delivery--bioavailability of naproxen from orally administered dextran-naproxen ester prodrugs varying in molecular size in the pig. Int. J. Pharm. 1989; 53:157-165.
21. Antonin, K.H., Bieck, P., Schurier, M., Jedrychowski, M., Malchow, H. Oxprenolol absorption in man after single bolus dosing into segments of the colon compared with that after dosing. Br. J. Clin. Pharmac., 1985; 19: 1375-1425
22. Chung, M., Ritberg, D.P., Gaffeney, M., Singleton, W., (). Clinical Pharmacokinetics of nifidepine, gastro intestinal therapeutic system –a controlled release formulation of nifidepine. Am. J. Medicine. 1987; 83, Suppl 6 B: 1014.
23. Rubinstein, A., Nakar, D., Sintov, A., (1992). Colonic drug delivery: enhanced release of indomethacin from cross-linked chondroitin matrix in rat cecal content. Pharm. Res., Feb; 9(2): 276-8.
24. Dew, M.J., Hughes, P.J., Lee, M.G., Evans, B .K., Rhodes, J., (). An oral preparation to release drugs in the human colon. Brit. J Clinical Pharmacology. 1982a; 14: pp. 405–408.
25. Klotz, U., Maier, K. E., Fischer, C., Bauer, K. H., (1985). A new slow-release form of 5-amino salicylic acid for the oral treatment of inflammatory bowel disease. Biopharmaceutical and pharmaceutical characteristics. Drug.Res. 35, 636-639.
26. MacNeil, M.E. and Stevens, H.N., (1990). Patent WO 90/09168.
27. Theeuwes, F., Yum, S., Haak, R., Wong, P., (1991). Systems for trigerred, pulsed, and programmed drug delivery. In: Temporal control of drug delivery. Hrushesky, W.; Langer, R.; Theeuwes, S. (Eds.). NY Acad Sci: New York, 428-440.
28. Harboe, E., Larsen, C., Johansen, M., Olesen, H.P., Macromolecular prodrugs. XV. Colon-targeted delivery--bioavailability of naproxen from orally administered dextran-naproxen ester prodrugs varying in molecular size in the pig. Int. J. Pharm. 1989; 53:157-165.
29. Ashford M, Fell JT, Attwood D, Sharma H, Woodhead PJ. Int J Pharm. 1993a; 95: 193-199.
30. Evans DF, Pye G, Bramley R, Hardcastle JD. Gut. 1988, 29:1035-1041
31. Takaya T, Ikada C, Imagawa N, Niwa K, Takada K. J Pharm Pharmacol 1995; 47:474- 478.
32. Saffron M, Kumar GS, Sabvariar C, Burnham JC, Williams F, Neckers DC. Science 1986; 233: 1081-1084.
33. Wilding IR, Davis SS, Bakhshaee M, Stevens HNE, Sparrow RA, Brennan J. Pharm Res 1992; 9: 654-657.
34. Sinha, V.R, Kumria, R., Binders for colon-specific drug delivery: an in vitro evaluation. Int. J. Pharm. 2002; 249: 23-31.
35. Morishita, I., Morishita, M., Takayama, K., Machida, Y., Nagai, T. Enteral insulin delivery by microspheres in three different formulations using Eudragit L100 and S100. Int. J. Pharm. 1993; 91: 29-37.
36. Patel, Ge., Patel, Gi., Patel, R., Patel, J., Bharadia, P., Patel, M., (2007). Sodium Alginate: Physiological Activity, Usage &Potential Applications. Drug Delivery technology, April Vol. 7 No. 4: 27-30.
37. Narayani, R., Rao, K.P., (1995). Polymer-coated gelatin capsules as oral delivery devices and their gastrointestinal tract behaviour in humans. J. Biomaterial Science Polymer Edition 7: 39-48.
38. Takaya T, Niwa K, Muraoka M, Ogita I, Nagai N, Yano R, Kimura G, Yoshikawa Y, Yoshikawa H, Takada K. Importance of dissolution process on systemic availability of drugs delivered by colon delivery system. J Control Rel. 1998; 50 (1-3):111-122.
39. Muraoka M, Hu Z, Shimokawa T, Sekino S, Kurogoshi R, Kuboi Y, Yoshikawa Y, Takada K. Evaluation of intestinal pressure-controlled colon delivery capsule containing caffeine as a model drug in human volunteers. J Control Rel 1998; 52(1-2):119-129.
40. Jeong Y, Ohno T, Hu Z, Yoshikawa Y, Shibata N, Nagata S, Takada K. Evaluation of an intestinal pressure-controlled colon delivery capsules prepared by a dipping method. J Control Rel 71(2):175-182.
41. Hay DJ, Sharma H, Irving MH. Spread of steroid containing foam after intrarectal administration. Brit Med J 1979; 1:1751-1753.
42. Watanabe S, Kawai H, Katsuma M, Fukui M. Colon specific drug release system. U. S. Patent, 1998, 09/183339.
43. Takemura S, Watanabe S, Katsuma M, Fukui M. Human gastrointestinal treatment study of a novel colon delivery system (CODES) using scintography, Pro Int Sym Control Rel Bioact Mat 2000; 27.
44. Masataka K, Watanabe S, Takemura S, Sako K, Sawada T, Masuda Y, Nakamura K, Fukui M, Connor AL, Wilding IR. Scintigraphic evaluation of a novel colon-targeted delivery system (CODESTM) in healthy volunteers. J Pharm Sci 2004; 93(5):1287-1299.
45. Theeuwes F, Guittared G, Wong P. Delivery of drugs to colon by oral dosage forms. U. S. Patent, 4904474
46. Swanson D, Barclay B, Wong P, Theeuwes F. Nifedipine gastrointestinal therapeutics system. Am J Med 1987; 8(6):3.
47. Philip AK, Pathak K. Osmotic flow through asymmetric membrane: A means for controlled delivery of drugs with varying solubility. AAPS PharmSciTech 2006; 7(3):1-11.
48. Ahmed IS. Effect of simulated gastrointestinal condition on drug release from pectin/ethyl cellulose as film coating for drug delivery to the colon. Drug Dev Ind Pharm 2005; 31(4-5): 465-470.

49. Cole ET, Scott RA, Connor AL, Wilding IR, Petereit HU, Schminke C, Beckert T, Cadé D. Enteric coated HPMC capsules designed to achieve intestinal targeting. Int J Pharm 2002; 231(1):83-95.

50. Mooter VG, Kinget R. Oral colon-specific drug delivery: A review: Drug Delivery 1995; 2:881-931.