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REVIEW ARTICLE

Colon Targeted Drug Delivery: A Review

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ABSTRACT

The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects. This review, mainly compares the primary approaches for CDDS (Colon Specific Drug Delivery) namely prodrugs, pH and time dependent systems, and microbially triggered systems, which achieved limited success and had limitations as compared with newer CDDS namely pressure controlled colonic delivery capsules, CODES^{TM}, and osmotic controlled drug delivery which are unique in terms of achieving in vivo site specificity, and feasibility of manufacturing process.

Keywords: Colon specific drug delivery, Time Clock system, Gamma scintigraphy.

INTRODUCTION

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]. The oral root is considered to be most convenient for administration of drugs to patient's dosage forms that deliver drugs into the colon rather than upper GIT prefers number of advantages. Oral delivery of drugs to the colon is valuable in the treatment of disease of drug in the upper GIT. The colon is reach in lymphoid tissue uptake of antigens into mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery. Additionally, the colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drug apart from retarding of targeting dosage forms.

Targeting of drugs to the colon by the oral route could be achieved by different approaches including matrix and coated systems, for which the drug release is controlled by the gastrointestinal pH, transit times or intestinal flora. The method by which the drug release will be triggered by the colonic flora appears to be more interesting with regard to the selectivity[2]. A number of synthetic azo polymers and natural or modified polysaccharides (chondroitin sulphate, guar gum, xanthan gum, locust gum, inulin, dextrans, starch, amylase, pectins) degraded by the human colonic flora, have thus been investigated as colonic drug delivery carriers[3].

Colon specific drug delivery has gained increased importance not just for the delivery of drugs for the treatment of local diseases associated with the colon but also as potential site for the systemic delivery of therapeutic proteins and peptides. To achieve successful colon targeted drug delivery, a drug needs to be protected from degradation, release and/or absorption in the upper portion of the GI tract and then ensure abrupt or controlled release in the proximal colon. Drug modifications through covalent linkages with carrier or prodrug approach and formulation based approaches can be used for colonic delivery.

The functional requirement of an oral colonic drug delivery system is to prevent drug release in the upper gastrointestinal regions and sensitivity to the trigger mechanism to ensure prompt drug release in the colon. The pH dependent approach for colonic drug delivery is based on the pH differential along the gastrointestinal tract with values increasing from about 1 to 2.5 in the

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stomach through 6.6 in the proximal small bowel to a peak of about 7.5 in the terminal ileum followed by a fall in pH to 6.4 in the colon. This concept utilizes polymeric carriers that are insoluble in the low pH media of the upper gastrointestinal tract, but dissolve at the higher, near neutral pH of the distal gut. Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing reduce side effect.

• To delay the drug absorption and hence sustained release.

• 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.

• Colon-specific drug delivery system is considered to be beneficial in the treatment of colon diseases. 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.

• Colon is a site where both local and systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, for example Ulcerative Colitis or Cohn's disease.

• 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 gastrointestinal tract, highly affected by hepatic metabolism.

ADVANTAGES OF COLON DRUG DELIVERY SYSTEM

• Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon (ulcerative colitis, Chron's disease, carcinomas and infections).

• Minimizing side effects that occur because of release of drugs in the upper GIT or unnecessary systemic absorption[4].

• 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[4].

Anatomy and Physiology of Colon

The large intestine extends from the distal end of the ileum to the anus. Human large intestine is about 1.5 m long[5]. The colon is upper five feet of the large intestine and mainly situated in the abdomen. The colon is a cylindrical tube that is lined by moist, soft pink lining called mucosa; the pathway is called the lumen and is approximately 2-3 inches in diameter. 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, sigmoid colon, rectum and the anal canal[6]. The physiology of the proximal and distal colon differs in several respects that have an effect on drug absorption at each site. The physical properties of the luminal content of the colon also change, from liquid in the cecum to semisolid in the distal colon.

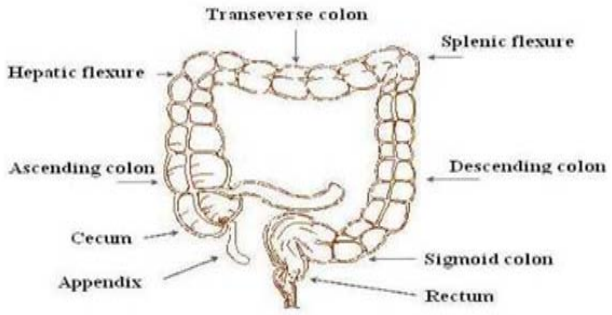

Figure:Structure of colon

GENERAL CONSIDERATIONS FOR DESIGN OF COLONIC FORMULATIONS:

Formulations for colonic delivery are, in general, delayed-release dosage forms which may be designed either to provide a 'burst release'[7] or a sustained/prolonged release once they reach the colon. The proper selection of a formulation approach is dependent upon several important factors, which are listed below.

a) Pathology and pattern of the disease, especially the affected parts of the lower GI tract or physiology and physiological composition of the healthy colon if the formulation is not intended for localized treatment.

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

c) The desired release profile of the active ingredient.

FACTORS CONSIDERED IN DESIGNING OF CDDS:

(1) pH in the colon
(2) GI-Transit
(3) Colonic microflora

pH in the Colon

The pH of the gastrointestinal tract is subject to both inter and intra subject variations. Diet, diseased state and food intake influence the pH of

the gastrointestinal fluid. The change in pH along the gastrointestinal tract has been used as a means for targeted colon drug delivery[8]. There is a pH gradient in the gastrointestinal tract with value ranging from 1.2 in the stomach through 6.6 in the proximal small intestine to a peak of about 7.5 in the distal small intestine. The pH difference between the stomach and small intestine has historically been exploited to deliver the drug to the small intestine by way of pH sensitive enteric coatings. There is a fall in pH on the entry into the colon due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides.

GI-Transit

Gastrointestinal transit is the time it takes for food to leave your stomach and travel through your intestines. Many factors can affect transit time, including your diet, medications, prior surgeries, gender, level of physical activity and stress level, as well as any chronic or acute illnesses that affect your gastrointestinal tract. It takes varying amounts of time for food to pass through the different areas of your intestinal tract, which includes the stomach, small intestine and large intestine. Most digestion takes place in the small intestine. It takes up to three hours for 50 percent of your food to traverse the small intestine, according to Bowen. Bile helps break down fat in the small intestine. Two types of movement aid in transit through the small intestine: segmentation contractions, which mix the chyme to break it down, and peristalsis, which moves the chyme through the small intestine. The chyme touches the sides of the intestine, where absorption occurs.

Colonic microflora

A large number of anaerobic and aerobic bacteria are present in entire length of human GI tract. Over 400 distinct bacterial species have been found, 20-30% of which are of genus bacteroides[9]. The upper region of the GIT has a very small number of bacteria and predominantly consists of gram positive facultative bacteria. The rate of microbial growth is greatest in proximal areas because of high concentration of energy source. The concentration of bacteria in human colon is 10^{11}- 10^{12} CFU/ml. The most important anaerobic bacteria are Bacteroides, Bifidobacteria, Eubacteria, Peptostreptococcus, Peptococcus, Ruminococcus and Clostridiums. The metabolic activity of microflora can be modified by various factors such as age, GI disease, and intake of drug and fermentation of dietary residues.

CRITERIA FOR SELECTION OF DRUG FOR COLONIC DRUG DELIVERY:

Drug candidate

Drugs which show poor absorption from the stomach as intestine including peptide are most suitable for CDDS. Drugs used in treatment of IBD, ulcerative colitis, diarrhoea and Colon cancers are ideal candidates for local colon delivery[10]. For example, metoprolol, nifidipine, doxorubicin etc.

Drug carrier

The selection of carrier for particular drug candidate depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. The factors such as chemical, nature, stability and partition coefficient of drug and the type of absorption enhancers chosen influence the carrier selection. The carriers which contain additives like polymers (may be used as matrices and hydro gels as coating agents) may influence the release properties and efficacy of the systems[11]. For example, aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond, oligo-peptide transporter for drugs captopril, lisinopril etc.

Table:Criteria for selection of drugs for CDDS[12, 13, 14]

Criteria	Pharmacological class	Non-peptide drugs	Peptide drugs
Drugs used for local effects in colon against GIT diseases	Anti-inflammatory drugs	Oxyprenolol,Metoprolol, Nifedipine	Amylin,Oligonucleotide
Drugs poorly absorbed from upper GIT	Antihypertensive and antianginal drugs	Ibuprofen,Isosorbides, Theophylline	Cyclosporine, Desmopressin
Drugs for colon cancer	Antineoplastic and antifolate drugs	Pseudoephedrine, Methotrexate \	Epoetin,
Drugs that degrade in stomach and small intestine	Peptides and proteins	Bromophenaramine,5-Flourouracil, Doxorubicin	Gonadoreline, Interferons
Drugs that undergo extensive first pass metabolism	Nitroglycerin and corticosteroids	Bleomycin, Nicotine	Protirelin, Saloatonin
Drugs for targeting	Antiarthritic and antiasthamatic drugs	Prednisolone, hydrocortisone,5-Amino-salicylic acid	Somatropin,

APPROCHES TO COLON SPECIFIC DRUG DELIVERY

1) Conventional Drug Delivery Approach
 (a) pH sensitive polymer coated drug delivery to colon
 (b) Delayed (Time controlled release system) release drug delivery to colon
 (c) Microbially triggered drug delivery to colon
  (i) Prodrug approach
  (ii) Azo-polymeric approach
  (iii) Polysaccharide based approach
2) Novel Drug Delivery Approach
 (a) Pressure controlled drug delivery system (PCDCS)
 (b) Novel colon targeted delivery system (CODES™)
 (c) Osmotic controlled drug delivery to colon (OROS-CT)

1) Conventional Drug Delivery Approach

(a) pH sensitive polymer coated drug delivery to colon:

The oral administered drugs to the colon are accomplished by:

- Coating with pH dependent polymers
- Coating with pH independent biodegradable polymers

Coating with pH dependent polymers

In these systems drugs can be formulated as solid dosage forms such as tablets, capsules and pellets and coated with pH sensitive polymers as an enteric coating. Widely used polymers are methacrylic resins (Eudragits) which are available in water soluble and insoluble forms. Eudragit L and S are copolymers of methacrylic acid and methacrylate. 5-aminosalicylic acid is commercially available as an oral dosage form coated with Eudragit L and S. Other colon specific delivery systems based on methacrylic resins are described for prednisolone, insulin and quinolones[15]. The pH-dependent systems exploit the generally accepted view that pH of the human GIT increases progressively from the stomach (pH 1-2 which increase to 4 during digestion), small intestine (pH 6 - 7) at the site of digestion and it increases to 7-8 in the distal ileum. The gamma scintigraphy technique becomes most popular technique to investigate the gastrointestinal performance of pharmaceutical formulations. Mostly used polymer most commonly used pH-dependent coating polymers are methacrylic acid copolymers, commonly known as Eudragit S more specifically Eudragit L and S. Eudragit L & Eudragit S are two forms of commercially available enteric acrylic resins. Both of them produce films resistant to gastric fluid. Eudragit L & S are soluble in intestinal fluid at pH 6 & 7 respectively. Eudragit L is available as an organic solution (Isopropanol), solid or aqueous dispersion. Eudragit S is available only as an organic solution (Isopropanol) and solid. Eudragit L100 and S100 are the copolymers of methacrylic acid and methyl methacrylate. Carboxyl polymer form salts and dissolve above pH 5.5 and disperse in water to form latex and thus avoid the use of organic solvents is the coating process. Eudragit L100-55 polymers with ionizable phthalic acid groups dissolve much faster and at a lower pH than those with acrylic or methacrylic acid groups[16]. Colon targeted drug delivery systems based on methycrylic resins has described for insulin, prednisolone, quinolones, salsalazine, cyclosporine, beclomethasone dipropionate and naproxane, Khan et al. prepared lactose-based placebo tablets and coated using various combinations of two methacrylic acid polymers, Eudragit L100-55 and Eudragit 100 by spraying from aqueous systems. The same coating formulations are then applied on tablets and evaluated for in vitro dissolution rates under various conditions.

Coating with pH independent biodegradable polymers

Drugs that are coated with the polymers, which are showing degradability due to the influence of colonic microorganisms, can be exploited in designing drugs for colon targeting in order to release an orally administered drug in the colon. The intestinal microflora has a large metabolic capacity and it appears that reduction of azo bonds is a general reaction of colonic bacteria. The azo polymers having a high degree of hydrophilicity were degraded by colonic bacteria[17]. The copolymers of styrene and 2-hydroxy mehyl methacrylate which were cross linked with divinyl azo benzene and N.N¹ bis (β -styrene sulphonyl) - 4, 4¹-diamino azo- benzene to coat oral dosage forms of insulin and vasopressin. On arrival at the colon the coating is degraded by bacterial azo reductases there by releasing the drug.

(b) Delayed (Time controlled release system) release drug delivery to colon

The time-dependent approach is also known as pulsatile release, delayed or sigmoidal release system. In this approach, drug release from the system occurs after a pre-determined lag time, which corresponds to time for the transit from mouth to colon. The lag time depends upon the size of dosage form and gastric motility associated with the pathological condition of the individual.

In general, time dependent formulations for colonic delivery contains pH dependent coating component because the transit of a formulation in the GI tract is largely influenced by the gastric emptying time. The coating is also used to prevent rapid swelling and disintegration in the upper GI tract since other controlled- release components based on the mechanism of swelling, osmosis or a combination of two are often included in the time-dependent release formulations.

Enteric-coated time-release press coated (ETP) tablets:

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, time release function) and an enteric coating layer (acid resistance function)[18]. Tablet does not release drug in stomach due to acid resistance of outer enteric coating layer. After gastric emptying, the enteric coating layer rapidly dissolves and intestinal fluid begins slowly erode the press coated polymer (HPC) layer and when erosion front reaches the core tablet, rapid drug release occurs since the erosion process takes a long time there is no drug release period (lag phase) after gastric emptying. The duration of lag phase controlled either by weight or composition of the polymer (HPC) layer[2].

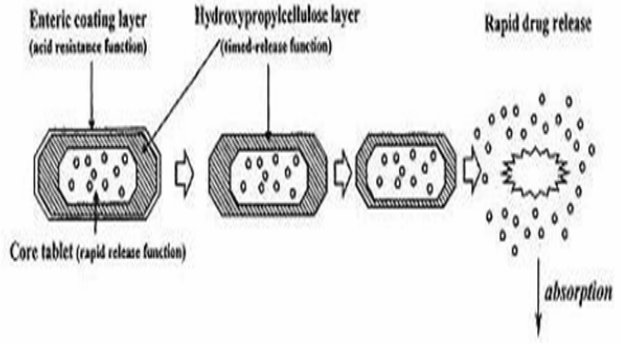

Figure 2: - Design of Enteric coated-timed release press coated tablets (ETP tablets)

(c) Microbially triggered drug delivery to colon

The microflora of the colon is in the range of 10^{11} -10^{12} CFU/ mL, consisting mainly of anaerobic bacteria, e.g. bacteroides, bifidobacteria, eubacteria, clostridia, enterococci, enterobacteria and Ruminococcus etc.[19] This vast microflora fulfills its energy needs by fermenting various types of substrates that have been left undigested in the small intestine, e.g. di- and tri-saccharides, polysaccharides etc.[20] For this fermentation, the microflora produces a vast number of enzymes like glucoronidse, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase. Because of the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon-specific drug delivery seems to be a more site-specific approach as compared to other approaches. These polymers shield the drug from the environments of stomach and small intestine and are able to deliver the drug to the colon. On reaching the colon, they undergo assimilation by micro-organism or degradation by enzyme or break down of the polymer back bone leading to a subsequent reduction in their molecular weight and thereby loss of mechanical strength[21]. They are then unable to hold the drug entity any longer.

(i) Prodrug approach:

Prodrug is pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in-vivo to release the active drug. For colonic delivery the prodrug are designed to undergo minimal absorption and hydrolysis in the tracts of upper GIT and undergo enzymatic hydrolysis in the colon, there by releasing the active drug moiety. Metabolism of azo compounds by intestinal bacteria is one of the most extensively studied bacterial metabolic processes[22]. Limitations of prodrug approach is that it is not very versatile approach as it's formulation depends upon the functional group available on the drug moiety for chemical linkage. Prodrugs of steroids having a hydroxyl group at C-21 position were prepared using poly-l-aspartic acid carrier. The ester prodrugs of dexamethasone with poly-l-aspartic acid when subjected to *in vitro* drug release studies in gastro intestinal tract homogenates released dexamethasone because of the cleavage of the ester bond by bacterial enzymes. The polymeric prodrugs of sulfasaslazine, is used in the treatment of ulcerative colitis and crohn's disease. Chemically sulfasaslazine is 5-aminosalicylic acid (5-ASA) coupled with sulphapyridine by azo bonding. On arrival at the colon the azo bond is reduced by colonic azo reductases to 5-ASA and sulphapyridne[23].

There are at least three factors that should be optimized for the site specific delivery of drugs by using the prodrug approach[24].

1. The prodrug must reach the target as early as possible, and uptake from the site must be fast and essentially perfusion rate limited.
2. Once the drug reached to the site, prodrug must be selectively liberated to the active drug relative to its conversion at other sites.

3. Once selectively liberated at the site of action, the active drug must be somewhat retained by the tissue.

Prodrugs can be designed to target specific enzymes or carriers by considering enzyme substrate specificity or carrier substrate specificity in order to overcome various unwanted drug properties.

Targeted prodrug design discussed in two categories:

1. Targeting specific enzymes and
2. Targeting specific membrane transporters.

Prodrug Design Targeting Enzymes:

In prodrug design, enzymes can be recognized as pre-systemic metabolic sites and an irreversible chemical modification technique is more successfully achieved to reduce the presystemic metabolism by targeting enzymes rather than by a prodrug approach. In the prodrug approach, site specific delivery can be obtained from tissue specific activation of a prodrug, which is the result of metabolism by an enzyme that is either exceptional for the tissue or present at a higher amount (compared with other tissues); thus, it activates the prodrug more competently. Recently, new therapies have been proposed to overcome the limitation of prodrug therapy[25].

These new approaches are referred to as:

ADEPT (antibody-directed enzyme prodrug therapy), and

GDEPT (gene-directed enzyme prodrug therapy), which attempt the localization of prodrug activation enzymes into specific cancer cells prior to prodrug administration.

(ii) Azo-polymeric prodrugs

Newer approaches are aimed at use of polymers as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers are used for this purpose. Subsynthetic polymers have been used to form polymeric prodrug with azo linkage between the polymer and drug moiety[26]. These have been evaluated for CDDS; various azo polymers have also been evaluated as coating materials over drug cores. These have been found to be similarly susceptible to cleavage by the azoreducatase in the large bowel. Coating of peptide capsules with polymers cross linked with azoaromatic group has been found to protect drug from digestion in the stomach and small intestine. In the colon the azo bonds are reduced and the drug is released[27].

Hydrogels[28]

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). 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.

(iii) Polysaccharide based delivery systems

Natural polysaccharides such as pectin and xylan are not digested in human stomach or small intestine, but are degraded in the colon by resident bacteria. Pectin in the form of compression coat was evaluated for targeting to colon. The coat was susceptible to enzymatic attack in the colon there by releasing the drug. They can be easily modified chemically, biochemically, and are highly stable, safe, nontoxic, hydrophilic and gel forming and in addition, are biodegradable. These include naturally occurring polysaccharides obtained from plant (guar gum, inulin), animal (chitosan, chondrotin sulphate), algal (alginates) or microbial (dextran) origin. The polysaccrides can be broken down by the colonic microflora to simple saccharides[29]. Therefore, they fall into the category of "generally regarded as safe" (GRAS).

2) Novel Drug Delivery Approach[30]

(a) Pressure controlled drug delivery system (PCDCs)

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. 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 a water-insoluble polymer capsule as a result of pressure in the lumen of the colon. The thickness of the ethylcellulose membrane is the most important factor for disintegration of the formulation[31]. 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. On oral administration they behave like an ethyl cellulose balloon because their base liquefies at body temperature. The reabsorbtion of water in colon causes the viscosity of luminal contents to increase, which directly affects the system via

colonic peristalsis. In response to raised pressure the capsule ruptures and releases the drug in the colon. 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 form. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to human[32].

(b) CODES™ (A Novel colon targeted delivery system)

CODES™ is a unique CDDS technology that was designed to avoid the inherent problems associated with pH or time–dependent systems. CODES™ is combined approach of pH dependent and microbially triggered CDDS. It has been developed by utilizing a unique mechanism involving lactulose, which acts as a trigger form site specific drug release in the colon. The system consists of 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 acid soluble material coating then protects the preparation as it passage through the alkaline pH of the small intestine. Once the tablet arrives in the colon the bacteria will 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[33].

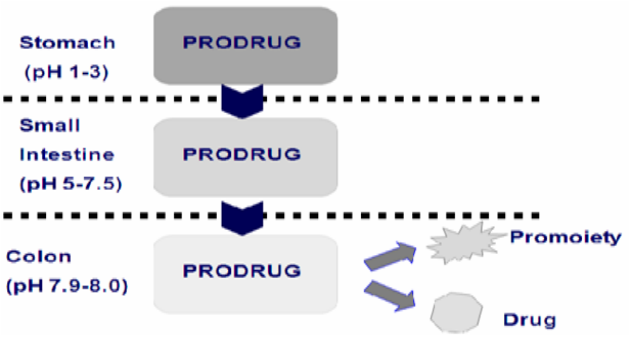

Figure 3: - Schematics of conceptual design of CODES™

(c) Osmotic controlled drug delivery (OROS-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[34]. 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 bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semi-permeable 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 enter the small intestine, the coating dissolve 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 semi-permeable membrane. 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.

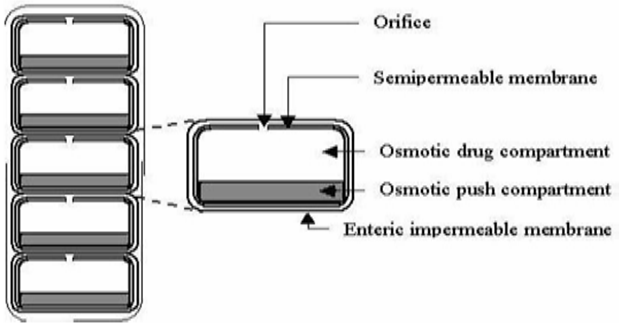

Figure 4: Cross-section of the OROS-CT colon targeted drug delivery system

EVALUATION OF COLON DRUG DELIVERY SYSTEM:

1. *Invitro*Evaluation

No 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 and physical stress and these factors make it difficult to design a slandered in vitro model.

In vitro model used for CDDS are:

a) 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. 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[35]. 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 7.4 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 (mean gastric emptying time), then one hour at pH 6.8, and finally at pH 7.4 (mean small intestine transit time) [36].

b) In vitro enzymatic test

For carrying out *In vitro* enzymatic test there are 2 tests:

1. Incubate carrier drug system in fermenter containing suitable medium for bacteria (*Streptococcus faccium* or *B.ovatus*) amount of drug released at different time intervals.
2. Drug release study is done in buffer medium containing enzymes (enzyme pectinase, dextranase), or rat or guinea pig or rabbit cecal contents. The amount of drug released in particular time is determined, which is directly proportional to the rate of degradation of polymer carrier.

2. *Invivo*Evaluation

In vivo methods offer various animal models. Guinea pigs were used to evaluate colon- specific drug delivery from a glucoside prodrug of dexamethasone. While choosing a model for testing a CDDS, relative model for the colonic diseases should also be considered. E.g. Guinea pigs are commonly used for experimental IBD model. The distribution of azo reductases and glucouronidase activity in the GIT of rat and rabbit is fairly comparable to that in the human. 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 vascularizes within 4 weeks, matures and becomes capable of developing of mucosal immune system from the host. *In vivo* gamma scintigraphic studies were carried out on the guar gum matrix tablets, using technetium 99 m- DTPA as a tracer. Scintigraphs taken at regular intervals have shown that some amount of tracer present on the surface of the tablets was released in stomach and small intestine. Radiotelemetry, roentenograpgy are the other *in vivo* evaluation methods for colon-specific drug delivery systems[37].

CURRENT AND FUTURE DEVELOPMENTS

Currently, there are several modified release solid formulation technologies available for colonic delivery. These technologies rely on GI pH, transit times, enterobacteria and luminal pressure for site-specific delivery. Each of these technologies represents a unique system in terms of design but has certain shortcomings, which are often related to degree of site-specificity, toxicity, cost and ease of scale up/manufacturing. It appears that microbially-controlled systems based on natural polymers have the greatest potential for colonic delivery, particularly in terms of site-specificity and safety. In this regard, formulations that employ a film coating system based on the combination of a polysaccharide and a suitable film forming polymer represents a significant technological advancement. Further developments in this area require means to improve the co-processing of the polymeric blend of a polysaccharide(s) and a film forming material while maintaining the propensity of the composition to microbial degradation in the colon.

REFERENCES

1. Akala EO, Elekwachi O, Chase V, Johnson H, Marjorie L, Scott K. Organic redox initiated polymerization process for the fabrication of hydrogels for colon specific drug delivery. Drug Dev Ind Pharm 2003; 29:375-386.
2. Rubunstein A. Microbially controlled drug delivery to the colon. Biopharm Drug Dispos 1990; 11:465-475.
3. Semde R., Amighi K., Pierre D., Devleeschouwer M.J., Moes A.J., "Leaching of pectin from mixed pectin: insoluble polymer films intended for colonic drug delivery", International Journal of Pharmaceutics, 174 (1998) 233–241.
4. Basit A, Bloor J. Perspectives on colonic drug delivery. Business briefing: PharmTech. 2003; 185-190.
5. Vandamme Th F and Chaumeil J C. The Use of Polysaccharides to Target drugs to the Colon, CarboPoly, 48, 2002:219-31.
6. Macfarlane GT and Cummings JH. The Colonic Flora, Fermentation and Large Bowel Digestive Function. In Phillips SF, Pemberton JH, Shorter RG. The Large Intestine: Physiology, Pathophysiology and Disease. New York: Raven press, 1991: 51.

7. Pinhasi, A., Gomberg, M., Avramoff, A.: US20046703044 (2004).
8. Thomas P and Rhodes J, Absorption of Delayed-release Prednisolone in Ulcerative Colitis and Crohn's Disease, Int J Pharm, 37, 1985: 757-61.
9. Tomlin J and Read NW. The Relation between Bacterial Degradation of Viscous Polysaccharides and Stool Output in Human Beings, Brit J Nutr., 60, 1988, 476.
10. Bussemer T, Otto, Bodmeier IR. Pulsatile Drug-Delivery Systems. Crit. Rev. There. Drug Carrier System. 2003, 18: 433-458.
11. Chavan, MS, Sant, VP and Nagarsenker MS. Azo-containing Urethane Analogues for Colonic Drug Delivery: Synthesis, Characterization and In Vitro Evaluation. Journal of Pharmacy Pharmacology. 2001; 53: 895-900.
12. Antonin KH, Rak R, Bieck PR, Preiss R, Schenker U, Hastewell J, Fox R, Mackay M, The absorption of human calcitonin from the transverse colon of man. Int J Pharm 1996; 130(1):33-39.
13. Fara JW. Novel Drug Delivery and its Therapeutic Application. In: Presscot LF, Nimmo WS, editors. Colonic drug absorption and metabolism. Wiley: Chichester, 1989; 103-120.
14. Mackay M, Tomlinson E. Colonic delivery of therapeutic peptides and proteins, In: Biek PR, editors. Colonic drug absorption and metabolism. New York: Marcel Dekker, 1993; 159-176.
15. Schacht E, Gevaert A, kenawy ER, Molly K Gelan J. Polymers for colon-specific drug delivery, Journal of controlled release, 39, 1996, 327-338.
16. Ramprasad Y V, Krishnaiah Y S, Satyanarayana S. Studies of guar gum compression-coated 5-aminosalicylic acid tablets for colon-specific drug delivery, Drug development and industrial pharmacy, 25(5), 1999, 651-657.
17. Davis SS, Hardy JG, Fara JW. Transit of pharmaceutical dosage forms through the small intestine. Gut. 1986; 27: 886-892.
18. Vassallo M, Camilleri M, Phillip SF, Brow ML, Chapman NJ, Thomforde GM. Transit through the proximal colon influences stool weight in the a irritable bowel syndrome. Gastroenterology 1992; 102:102-108.
19. Cummings JH, Englyst HN. (1987) Fermentation in the human large intestine and available substrates. Am J Clin Nutri 1987; 45:1243-1255.
20. Scheline RR. Metabolism of foreign compounds by gastrointestinal microorganisms. Pharmacol Rev 1973; 25:451-523.
21. Swift G. Biodegradable polymers in the environment: are they really biodegradable. Proc ACS Div Poly Mat Sci Eng 1992; 66:403-404.
22. Sinkula A A, Yalkowsky S H. Rationale for design of biologically reversible drug derivatives: prodrugs, J Pharm Sci., 64, 1975, 181-210.
23. D'Acquisto F, May M J, Ghosh S. An emerging theme in anti-inflammatory therapies, Mol. Intervent., 2, 2002, 22–35.
24. Stella V J, Charman W N, Naringrekar V H. Prodrugs, Inc.: Do they have advantages in clinical practice? Drugs, 29, 1985, 455-473.
25. Higuchi T, Stella V (ed.). Prodrugs: an overview and definition. Inc.: Prodrugs as Novel Drug Delivery Systems, ACS Symposium Series, Washington, DC: American Chemical Society, 1975, 1-115.
26. Kinget R, Van-Den-Mooter G, Samyn C. Azopolymers for colon-specific drug delivery, Part 44. Influence of the type of azopolymer on degradation by intestinal microflora, International journal of Pharmaceutics, 93, 1993, 133-139.
27. Bronsted H, Hovgaard L, Simonsen L. Dextran hydrogels for colon-specific drug delivery, Part 3. In vitro and in vivo degradation, STP-Pharm-Sciences, 5(1), 1995, 60-64.
28. Ashord M, Fell JT, Attwood D, Sharma H, Woodhead P. An evaluation of pectin as a carrier for drug targeting to the colon. J Control Rel 1993; 26:213- 220.
29. Fukui E, Miyamura N, Verma K, Kobayashi M. Preparation of enteric coated time released press coated tablets and evaluation of their function by in vitro and in vivo tests for colon targeting. International Journal of Pharmaceutics. 2000; 204: 7-15.
30. Gazzaniga A, Iamartino P, Maffino G,Sangalli ME. Oral delayed release system for colonic specific drug delivery. International Journal of Pharmaceutics. 1994; 108: 77-83.
31. Hata T, Shimazaki Y, Kagayama A, Tamura S, Ueda S. Development of a

novel drug delivery system, time-controlled explosion system (TES). Part 5 Animal pharmacodynamic and human bioavailability studies. International Journal of Pharmaceutics. 1994; 110: 1-7.

32. Evans DF, Pye G, Bramley R, Clark AG, Dyson TJ, Hardcastle JD. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Gut. 1988; 29: 1035-1041.
33. Yang L, James S, Joseph A. Colon specific drug delivery new approaches and in vitro/ in vivo evaluation. Int J Pharm 2002; 235:1 -15.
34. 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.
35. Cole ET, Scott RA, Connor AL, Wilding IR, Petereit HU, Schminke C, Beckert T, CadéD. Enteric coated HPMC capsules designed to achieveintestinal targeting. Int J Pharm 2002; 231(1):83-95.
36. Fukui E, Miyamura N, Kobayashi M. An in vitro investigation of the suitability of presscoated tablets with hydroxypropyl methylcellulose acetate succinate (HPMCAS) and hydrophobicn additives in the outer shell for colon targeting. Journal of Controlled Release. 2001; 70: 97-107.
37. Breimer D D. Future challenges for drug delivery, J Control Rel 62, 1999 3-6.