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COLON SPECIFIC DRUG DELIVERY SYSTEM: REVIEW ON NOVEL APPROACHES

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ABSTRACT

Article reviews the research focus on potential opportunities and challenges available in new area of colon targeted drug delivery system. Colon was considered as "BLACK BOX" as, most of drugs are absorbed from upper part of GIT tract. Targeted drug delivery to the colon would ensure direct treatment at the disease site, lowering of dose and lesser systemic side effects. In addition, the colon can also be utilized as a portal for the entry of drugs into the systemic circulation. This review, mainly compares the primary approaches for CDDS (Colon Specific Drug Delivery) namely pro drugs, 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, CODESTM, and osmotic controlled drug delivery which are unique in terms of achieving *in vivo* site specificity,and feasibility of manufacturing process.

INTRODUCTION: Drug delivery to the colon is beneficial not only for the oral delivery of proteins and peptide drugs (degraded by digestive enzymes of stomach and small intestine) but also for the delivery of low molecular weight compounds which are used to treat diseases associated with the colon or large intestine such as ulcerative colitis, diarrhoea, and colon cancer. The colon has a long retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.

It is a serious drawback in the conditions where localized delivery of the drugs in colon is required or in conditions where a drug is needed to be protected from hostile environment of upper GIT. Colon is rich in lymphoid tissue, eg., Uptake of antigen into mast cells of colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery. Region of colon is recognized as having a somewhat less hostile environment with less diversity and intensity of activity than stomach and Small intestine [1, 3].

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 (Crohn's disease and ulcerative colitis), irritable bowel syndrome, and colon cancer. Potential applications of colonic delivery include chronotherapy, prophylaxis of colon cancer and treatment of nicotine addiction. 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. 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.

Because of the high water absorption capacity of the colon, the colonic contents are considerably viscous and their mixing is not efficient, thus availability of most drugs to the absorptive membrane is low. Among the various reactions carried out by these gut flora, azo reduction and enzymatic cleavage are common. 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. The various colon targeting disease, drugs and site of action are given in **table 1** [2, 7].

TABLE 1: COLON TARGETING DISEASES, DRUGS AND SITES [3, 2, 5]

Target sites	Disease conditions	Drug and active agents
Topical action	Inflammatory bowel disease	Hydrocortisone
	Irritable bowel disease,	Budesonide
	Crohn's disease,	Prednisolone, sulfasalazine
	Chronic pancreatitis	Osalazine, mesalazine
Local action	Cystic fibrosis	Digestive enzyme
	Colorectal cancer	5-flurouracil
Systemic action	Gastric irritation	NSAID's
	Oral delivery of peptides	Insulin
	Oral delivery of vaccine	typhoid

Need of Colon Targeted Drug Delivery [3]:

- Direct treatment at the disease site, lower dosing and fewer systemic side effects.
- Site-specific or targeted drug delivery system, colon-specific formulation could also be used to prolong the drug delivery.
- Beneficial in the treatment of colon diseases.
- Both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease.
- 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 are susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism.

Colon anatomy [6]:

1) The GI tract is divided into stomach, small intestine and large intestine. The large intestine extending from the ileocecal junction to the anus is divided in to three main parts. These are the colon, the rectum and anal canal. Measure of different parts of colon is given in **table 2**.

TABLE 2: MEASURES OF DIFFERENT PARTS OF COLON [6, 7, 12]

Large Intestine	Length (cm)
Cecum	6-9
Ascending colon	20-25
Descending colon	10-15
Transverse colon	40-45
Sigmoid colon	35- 40
Rectum	12
Anal canal	3

2) The entire colon is about 5 feet (150 cm) long, and is divided in to five major segments. Peritoneal folds called as mesentery which is supported by 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 contain the left half of the transverse colon, descending colon, splenic flexure and sigmoid. The rectum is the last anatomic segment before the anus. The human intestine and colon were shown in **Figures 1 and 2** given below.

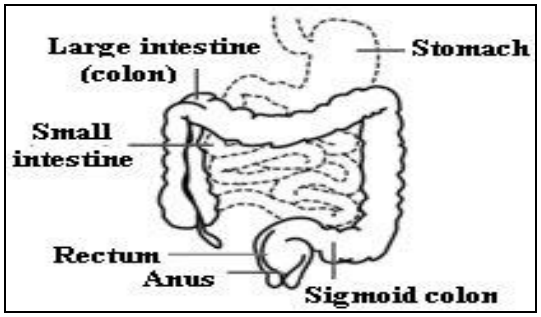

FIGURE 1: STRUCTURE OF HUMAN INTESTINE

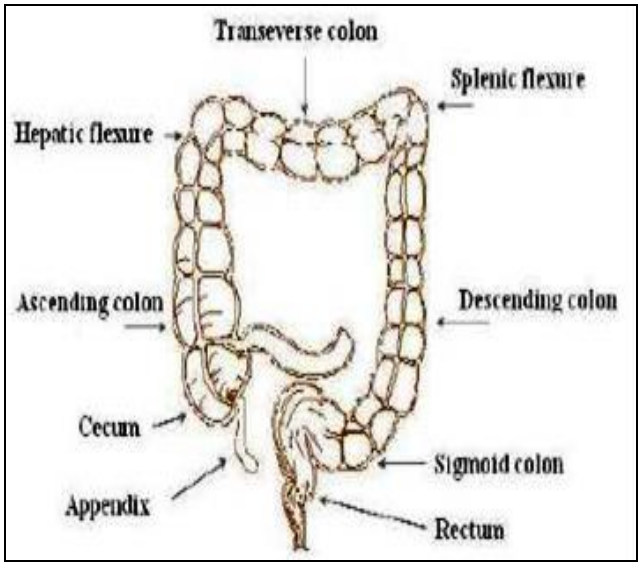

FIGURE 2: STRUCTURE OF COLON

3) The major function of the colon is the creation of suitable environment for the growth of colonic microorganisms, storage reservoir of faecal contents, expulsion of the contents of the colon at an appropriate time and absorption of potassium and water from the lumen. The absorptive capacity is very high, each about 2000ml of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed.

pH differences in the colon: On entry in to the colon, the pH dropped to 6.4 ± 0.5. The pH in the mid colon was found to be 6.6 ± 1 and in the left colon, 7.0 ± 1.

Gastrointestinal Transit: Gastric emptying of dosage form is highly variable and depends primarily on whether the subject is fed or fasted and on the properties of the dosage form such as size and density. G.I transit time of different parts is given below in **table 3**. Diseases affecting colonic transit have important implications for drug delivery, diarrhea increases colonic transit and constipation decreases it. The digestive motility pattern takes place when food is present in the stomach. It is said by regular, frequent contractions (about 4-5/min.) which affect the mixing intestinal contents and moving them towards the colon in short segments and lasts as long as food remains present in the stomach. The most frequent movements seen in the colon are very slow segmenting movements that typically occur every 30 minutes [7, 12].

TABLE 3: GASTROINTESTINAL TRANSIT TIME OF CONTENTS [6, 7]

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

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 adeno suppression, immune suppression, 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.

Criteria for Selection of Drug for CDDS [9, 11]: The best Candidates for CDDS are drugs which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of IBD, ulcerative colitis, diarrhea, and colon cancer are ideal candidates for local colon delivery. The criterion for selection of drugs is summarized in **Table 4** given below. Drug Carrier is another factor which influences CDDS. The selection of carrier for particular drugs depends on the physiochemical nature of the drug as well as the disease for which the system is to be used.

TABLE 4: SELECTION OF DRUGS [3, 9 11, 18]

Criteria	Pharmacological class	Non-peptide drug	Peptide drug
For local effects on colon	Anti-inflammatory drugs	Oxprenolol, metoprolol, nifedipine	Amylin, oligonucleotide
Poor absorption in upper g.i.t	Antihypertensive and antianginal drugs	Ibuprofen, isosorbides, theophylline	Cyclosporine, desmopressin
For colon cancer	Antineoplastic drugs	Pseudoephedrine	Epoetin, glucagon
Drugs for targeting	Antiarithritic and antiasthmatic drugs	Prednisolone, hydrocortisone, 5-amino-salicylic acid	Somatropin, urotoiletin

Factors such as chemical nature, stability and partition coefficient of the drug and type of absorption enhancer chosen 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.

Targeting mechanism of drug acting on Colon:

1) PH- dependent delivery
2) Time dependent delivery
3) Pressure dependent delivery
4) Bacteria dependent delivery

pH- dependent Delivery [4, 9, 18]: In the stomach, pH ranges between 1 and 2 during fasting but increases after eating. The pH is about 6.5 in the proximal small intestine and about 7.5 in the distal small intestine. From the ileum to the colon, pH declines significantly. It is about 6.4 in the cecum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers. The pH in the transverse colon is 6.6 and 7.0 in the descending colon. Use of pH dependent polymers is based on these differences in pH levels.

The polymers described as pH dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises. Although a pH dependent polymer can protect a formulation in the stomach, and proximal small intestine, it may start to dissolve in the lower small intestine, and the site-specificity of formulations can be poor. The decline in pH from the end of the small intestine to the colon can also result in problems, lengthy lag times at the ileocecal junction or rapid transit through the ascending colon which can also result in poor site-specificity of enteric-coated single-unit formulations.

Pre-sensitive enteric coatings have been used routing to deliver drugs to small intensive. These polymer coatings are insensitive to the acidic conditions of stomach yet dissolve at the higher pH environment of small intestine. This pH differential principle has also been attempted for colonic delivery purposes although polymers used for solenoid targeting and to have a threshold pH for dissolution that is higher than those used in conventional enteric coating applications. Most commonly co-polymers of methacrylic acid and methyl methacrylate that dissolve at pH 5- pH 7 have been investigated. This approach is based on assumption that G.I pH increases progressively from the small intestine to colon. In fact, the in distal small intestine is usually around 7.5, while the pH in proximal colon is closer to 6. These delivery systems therefore have a tendency to release their drug load prior to reaching colon. To overcome the problem of premature drug release a copolymer of methacrylic acid, methyl methacrylate has been developed recently.

The inter subject variability may be due to various reasons such as electrolyte concentration and transit time will therefore impact on in vivo behavior of pH responsive systems, ranging from early drug release is small intensive to are release at all with the formulation passing throughout gut intact. The latter situation will also arise when pH of colon and possibility the small intensive is considerably lower than normal as the case in patients with creative qualities. In spite of their limitations, pH sensitive delivery systems are commercially available for mesalazine in and budesonide for treatment of ulcerative colitis & Crohn's disease, respectively. The pH values of commonly used polymers are given in **table 5**.

TABLE 5: THRESHOLD pH OF COMMONLY USED ENTERIC POLYMERS [4, 9, 14]

Enteric polymer	Optimum pH for dissolution
Poly vinyl acetate phthalate	5.0
Cellulose acetate trimelitate (CAT) 5.5	5.5
Hydroxypropyl methylcellulose phthalate (HPMCP)	5.5
Hydroxypropylmethylcellulose acetate succinate (HPMCAS)	6.0
Methacrylie acid copolymer, Type C (Eudragit L100-55)	6.0
Methacrylic acid copolymer dispersion (Eudragit L30D-55)	5.0
Methacrylic acid copolymer, Type A	6.0
Eudragit®L-100 and Eudragist L12,5	---
Cellulose acetate phthalate (CAP) (Aquateric)	6.0
Methacrylic acid copolymer, Type B	7.0
Eudragist S-100 and Eudragit S12, 5	---
Shellac (Mar coat 125 & 125 N)	7.0

Time Dependent Delivery [3, 11]: 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 colonical availability. 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.

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.

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. 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. 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). 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. Design of time dependent delivery system is given in **figure 3 and 4**.

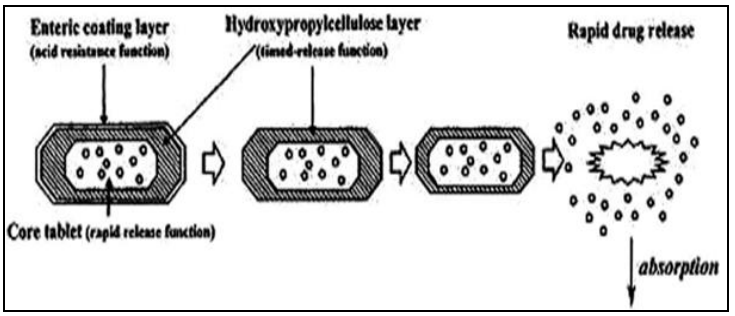

FIGURE 3: DESIGN OF ENTERIC COATED TIMED-RELEASE PRESS COATED TABLET

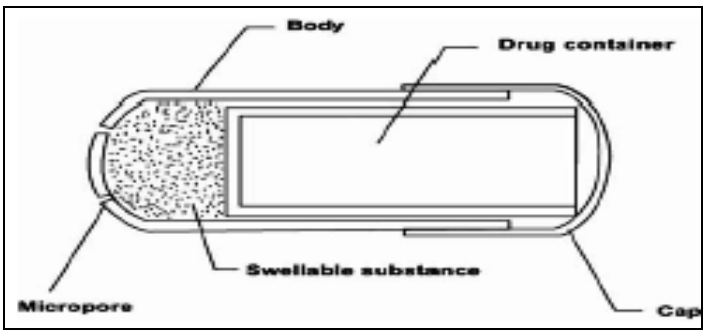

FIGURE 4: TIME CONTROLLED OR TIME DEPENDENT SYSTEM

Microbially Triggered Drug Delivery to Colon [10, 3, 5]: The microflora of the colon is in the range of 1011 - 1012 CFU/mL, consisting mainly of anaerobic bacteria, e.g. bacteroides, bifidobacteria, eubacteria, clostridia, enterococci, enterobacteria and ruminococcus etc. 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.

For this fermentation, the microflora produces a vast number of enzymes like glucoronidase, 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. They are then unable to hold the drug entity any longer.

(i) Prodrug Approach for Drug Delivery to Colon: Prodrug is a 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 is designed to undergo minimal hydrolysis in the upper tracts of GIT, and undergo enzymatic hydrolysis in the colon there by releasing the active drug moiety from the drug carrier. Metabolism of azo compounds by intestinal bacteria is one of the most extensively studied bacterial metabolic processes. A number of other linkages susceptible to bacterial hydrolysis especially in the colon have been prepared where the drug is attached to hydrophobic moieties like amino acids, glucoronic acids, glucose, glactose, cellulose etc.

(ii) Azo-Polymeric Prodrugs: Newer approaches are aimed at the use of polymers as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers have been used for this purpose. Sub synthetic polymers have been used to form polymeric prodrug with azo linkage between the polymer and drug moiety. 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 azo reducatase in the large bowel. Coating of peptide capsules with polymers cross linked with azo aromatic group has been found to protect the drug from digestion in the stomach and small intestine. In the colon, the azo bonds are reduced, and the drug is released.

(iii) Polysaccharide Based Delivery Systems: The use of naturally occurring polysaccharides is attracting a lot of attention for drug targeting the colon since these polymers of monosaccharides are found in abundance, have wide availability are inexpensive and are available in a variety of structures with varied properties. 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 polysaccharides can be broken down by the colonic microflora to simple saccharides. Therefore, they fall into the category of "generally regarded as safe" (GRAS).

Pressure Controlled Drug-Delivery Systems [16, 7, 13]: 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. 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.

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 ethylcellulose single unit capsules the drug is in a liquid. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to humans.

Novel Colon Targeted Delivery System (CODES^{TM}) [1, 3, 5, 9]: CODES^{TM} is a unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems. CODES^{TM} 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 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. 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. Design of CODES^{TM} delivery system is given in **figure 5**.

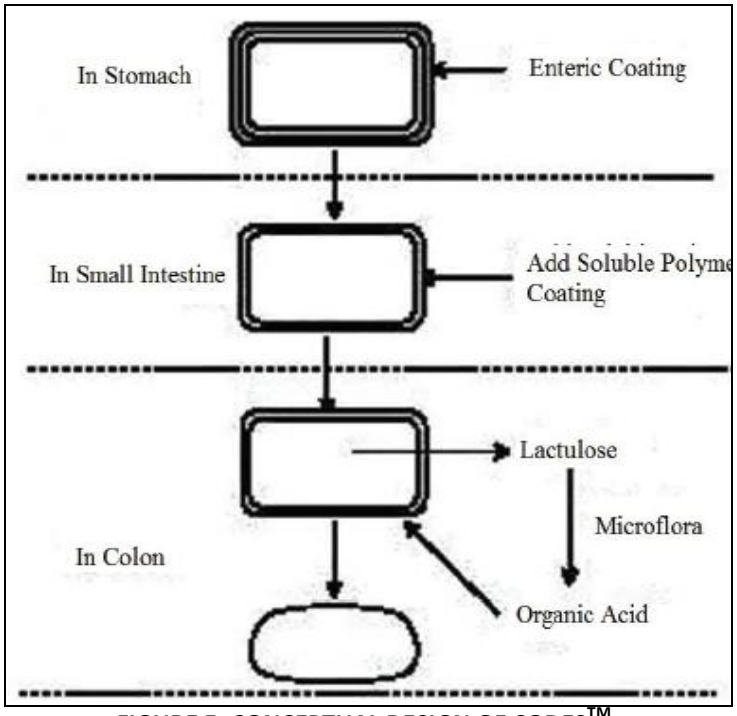

FIGURE 5: CONCEPTUAL DESIGN OF CODES^{TM}

Osmotic Controlled Drug Delivery (ORDS-CT) [11]: 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. 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.

Each bi-layer 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 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 semi permeable 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. Various in vitro / in vivo evaluation techniques have been developed and proposed to test the performance and stability of CDDS. Design of ORDS-CT is given in figure 6.

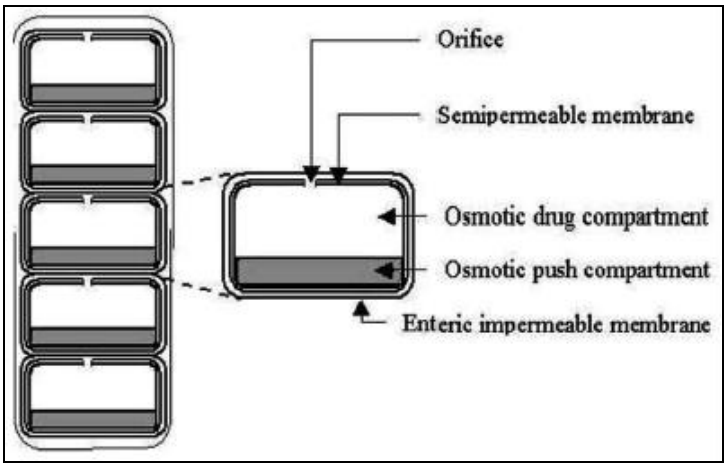

FIGURE 6: OSMOTICALLY CONTROLLED SYSTEM

Pulsatile Drug Delivery System [2, 6, 17]: A pulsatile drug release, where the drug is released rapidly after a well defined lag-time, could be advantageous for many drugs or therapies. Pulsatile release systems can be classified in multiple-pulse and single-pulse systems. A popular class of single-pulse systems is that of rupturable dosage forms. Other systems consist of a drug-containing core, covered by a swelling layer and an outer insoluble, but semi permeable polymer coating or membrane. The lag time prior to the rupture is mainly controlled by:

1) The permeation and mechanical properties of the polymer coating.

2) The swelling behavior of the swelling layer. As is frequently found in the living body, many vital functions are regulated by pulsed or transient release of bioactive substances at a specific site and time.

Methods for Pulsatile Drug Delivery System:

Capsular System: Single unit systems are mostly developed in capsule form. The lag time is continued by a plug, which gets pushed away by swelling or erosion, and the drug is released as a pulse from the insoluble capsule body. The design of capsular system is given in **figure 7**.

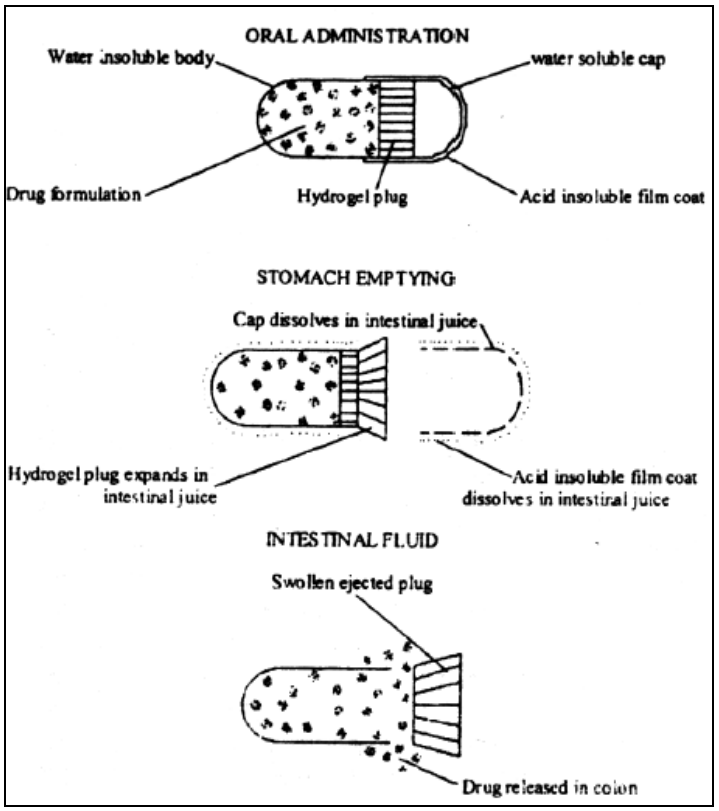

FIGURE 7: CAPSULAR SYSTEM

Osmotic System [8, 14]: This system consists of a capsule coated with a semi permeable membrane. Inside the capsule was an insoluble plug consisting of osmotically active agent and the drug formulation. This system shows good *in-vivo* and *in-vitro* correlation in humans and used to deliver methylphenidate to school age children for the treatment of Attention Deficit Hyper activity Disorder (ADHD), e.g.: Port® System. Another system is also based on expendable orifice that contain capsular system in which liquid drug is absorbed on highly porous particles. Drug releases through orifice of a semi permeable capsule supported by an expending osmotic layer after the barrier layer is dissolved. The Port® System (Port Systems, LLC) consists of a gelatin capsule coated with a semi permeable membrane (e.g., cellulose acetate) housing an insoluble plug (e.g., lipidic) and an osmotically active agent along with the drug formulation .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 drug release pattern of port system is given in **figure 8**.

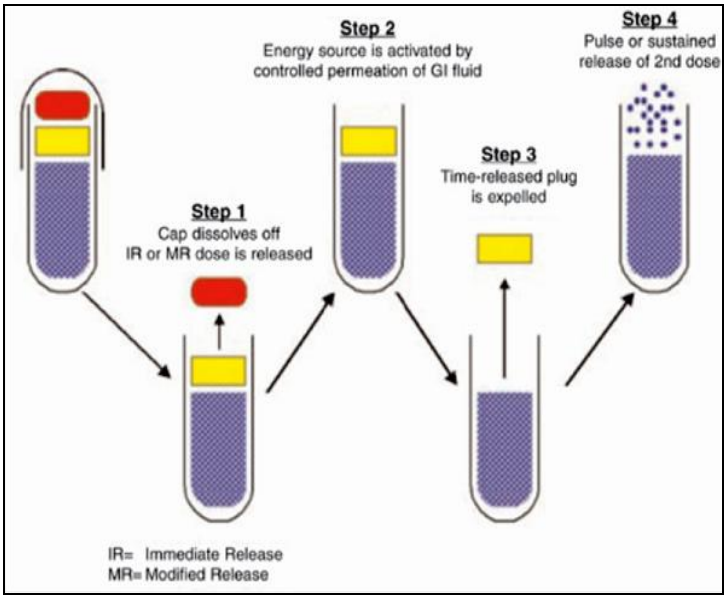

FIGURE 8: DRUG RELEASE PATTERN FROM PORT SYSTEM

Covalent linkage of the drug with a Carrier [6]: It involves the formation of a covalent linkage between drug and carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine. This approach chiefly involves the formation of prodrug, which is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in the biological environment to release the active drug. Formation of prodrugs has improved delivery properties over the parent drug molecule. The problem of stability of certain drugs from the adverse environment of the upper GIT can be eliminated by prodrug formation, which is converted into parent drug molecule once it reaches into the colon.

Azo Bond Conjugates [12]: The intestinal microflora is characterized by a complex and relatively stable community of microorganism, many with physiological functions, which play vital roles in health and disease. In addition to protection of the patient against colonization of the intestinal tract by potentially pathogenic bacteria, the indigenous microflora are responsible for a wide variety of metabolic processes, including the reduction of nitro and azo groups in environmental and therapeutic compounds.

Sulphasalazine was introduced for the treatment of rheumatoid arthritis and anti-inflammatory disease. Chemically it is salicylazosulphapyridine (SASP), where sulfapyridine is linked to a salicylate radical by an azo bond. When taken orally, only a small proportion of the ingested dose is absorbed from the small intestine and the bulk of the sulphasalazine reaches the colon intact. There it is split at the azo bond by the colonic bacteria with the liberation of sulphapyridine (SP) and 5 ASA. However sulphapyridine is seems to be responsible for most of the side effects of sulphasalazine and hence various new approaches for the treatment of IBD have emerged.

Glycoside Conjugates [5]: Steroid glycosides and the unique glycosidase activity of the colonic microflora from the basis of a new colon targeted drug delivery system. Drug glycosides are hydrophilic and thus, poorly absorbed from the small intestine. Once such a glycoside reaches the colon it can be cleaved by bacterial glycosidases, releasing the free drug to be absorbed by the colonic mucosa.

The major glycosidases identified in human feces are:

1) D-galactosidase,
2) D glucosidase,
3) L-arabinofuranosidase,
4) D-xylopyranosidase

These enzymes are located at the brush border and hence access to the substrate is relatively easy. In the plant kingdom numerous compounds are found as glycosides. Certain drugs act as glycon and can be conjugated to different sugar moieties which results in the formation of glycosides. Due to the bulky and hydrophilic nature of these glycosides, they do not penetrate the biological membrane upon ingestion.

Glucuronide Conjugates [1, 3]: Glucuronide and sulphate conjugation is the major mechanisms for the inactivation and preparation for clearance of a variety of drugs. Bacteria of the lower GIT, however, secrete glucuronidase and can deglucuronidate a variety of drugs in the intestine. Since the deglucuronidation process results in the release of active drug and enables its re-absorption, glucuronide prodrugs would be expected to be superior for colon targeted drug delivery.

Cyclodextrin Conjugates [2, 5]: Cyclodextrins (CyDs) are clyclic oligosaccharides consisted of six to eight glucose units through 1,4 glucosidic bonds and have been utilized to improve certain properties of drugs such as solubility, stability and bioavailability. The interior of these molecules is relatively lipophilic and the exterior relatively hydrophilic, they tend to form inclusion complexes with various drug molecules. They are known to be barely capable of being hydrolyzed and only slightly absorbed in passage through the stomach and small intestine; however, they are fermented by colonic microflora into small saccharides and thus absorbed in the large intestine.

Because of their bioadaptability and multi functional characteristics, CyDs are capable of alleviating the undesirable properties of drug molecules in various routes of administration through the formation of inclusion complexes. In an oral drug delivery system, the hydrophilic and ionizable CyDs can serve as potent drug carriers in the immediate release and delayed release formulations, respectively, while hydrophobic CyDs can retard the release rate of water-soluble drugs.

Since, CyDs are able to extend the function of pharmaceutical additives, the combination of molecular encapsulation with other carrier materials will become effective and a valuable tool in the improvement of drug formulation. Moreover, the most desirable attribute for the drug carrier is its ability to deliver a drug to a targeted site; conjugates of a drug with CyDs can be a versatile means of constructing a new class of colon targeting prodrugs.

Polymeric Prodrugs [3]: Azo-linked polymeric prodrugs of 5-ASA were prepared and evaluated in simulated human intestinal microbial ecosystem. Polyamides

containing azo grups in the backbone were prepared and tested in vitro in a reductive buffer or in the bioreactor medium. It was demonstrated that for the hydrophobic polymer, reduction stops at the hydrazine stage whereas for a hydrophilic analogue reduction with formation of amine occurred. The amount of the drug released depends on the nature of the polymer and can approach that of low molecular weight prodrugs.

Amino-Acid Conjugates [3, 5]: Due to the hydrophilic nature of polar groups like NH_2 and COOH, that is present in the proteins and their basic units, they reduce the membrane permeability of amino acids and proteins. Various prodrugs have been prepared by the conjugation of drug molecules to these polar amino acids. Non-essential amino acids such as tyrosine, glycine, methionine and glutamic acid were conjugated to SA.

The salicyluric acid was found to be metabolized to SA by the microorganisms of the intestinal flora of rabbit and dog. The prodrug was absorbed into the systemic circulation from the upper GIT and hence it was proved unsuitable for delivery of drugs to the colon. By increasing the hydrophilicity and chain length of the carrier amino acid and decreasing the membrane permeability of conjugates. This conjugate showed splendid results with minimal absorption and degradation in the upper GIT and proved suitable for colon targeted delivery of SA.

Opportunities in colon targeted drug delivery [2, 9, 15]

- 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, but also for systemic delivery of drugs like proteins and peptides, which are degraded and/or poorly absorbed in the stomach and small intestine.
- This is also a potential site for the treatment of diseases sensitive to circadian rhythms such as asthma, angina and arthritis. 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 reduces 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 (due to instability in the GI tract).
- The bioavailability of protein drugs delivered at the colon site needs to be addressed.

CONCLUSIONS: Drug targeting to the diseased colon are advantageous in reduced systemic side effects, lower dose of drug, supply of the drug only when it is required and maintenance of the drug in its intact form as close as possible to the target site. Successful colonic delivery could be achieved by protecting the drug from absorption and /or the environment of the upper GIT and then be abruptly released into the proximal colon, which is considered the optimum site for colon targeted delivery of drugs. The various strategies for targeting orally administered drugs to the colon include coating with pH-sensitive polymers, formulation of timed released systems, exploitation of carriers that are degraded specifically by colonic bacteria, bio-adhesive systems. All the approaches provide means for treatment of local diseases associated with the colon or for systemic absorption of poorly absorbable drugs. The colon is rich in microflora, which can be used to target the drug release in the colon.

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