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# Colon Targeted Drug Delivery Systems: A Review on Primary and Novel Approaches

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ABSTRACT

A colon is a site where local drug delivery takes place. Local delivery allows topical treatment of inflammatory bowel diseases. However, treatment can be effective if the drugs are not directed directly at the colon, thus reducing the side effects of the system. This review, in particular compares the main CDDS (Colon Specific Drug Delivery) methods namely prodrugs, pH and time-based systems, and pathogen-based systems, which have achieved limited success and limitations compared to the new CDDS i.e. pressure-controlled colon delivery pills, CODESTM, as well as the delivery of different osmotic-controlled drugs through vivo site specifications, as well as the feasibility of the production process.

## Introduction

Targeted drug delivery to the colon is highly desirable in the local treatment of various intestinal diseases such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, local treatment of colonic pathologies, and systematic delivery of protein and peptide drugs. The colon delivery system (CDDS) must be able to protect the colon-directed drug which means that drug withdrawal and absorption must not occur in the stomach and intestines, and the bioactive agent should not be reduced to any dispersed but only released and absorbed once the system reaches the colon.3 Colon is believed to be an ideal site for the reduction of peptides and protein drugs for the following reasons; (i) small differences, and the strength of digestive enzymes, (ii) the proteolytic activity of the colon mucosa is much lower than that observed in the small intestine, so CDDS protects peptide drugs from hydrolysis, and degradation of enzymatic to the duodenum and jejunum, and eventually converts the drug into ileum or colon which leads to greater systemic exposure.4 And finally, because the colon has a long shelf life of up to 5 days and is highly responsive to absorption enhancements.5 The oral route is also a very simple method and preferred but other CDDS routes can be used. Rectal administration provides a very short route for drug identification in the colon. However, reaching the nearest part of the colony through column management is difficult. Rectal administration is also uncomfortable for patients and compliance may be less than ideal.6 Prescription drug administration of prescribed medications offered as solutions, foam, and suppositories. The intrarectal route is used both as a means of systemic relaxation and the delivery of an overactive drug in the large intestine. Corticosteroids such as hydrocortisone and prednisolone are given in rectum treatment Review Article Abstract Colon is a site where local and systemic drug delivery is possible. Local delivery allows topical treatment of inflammatory bowel diseases. However, treatment can be effective if the drugs are not directed directly at the colon, thus reducing the side effects of the system. This review, in particular compares the main CDDS (Colon Specific Drug Delivery) methods namely prodrugs, pH and time-dependent systems, and pathogen-based systems, which have achieved limited success and limitations compared to the new CDDS i.e. pressure-controlled colon delivery pills, CODES, as well as the delivery of alternative osmotic-controlled drugs through vivo site details, as well as the production process of the Department of Medicine, Pharmacy School, Nizwa University, Birkat Al Mouz, Nizwa-616, Sultanate of Oman. Received: 07 Feb 2010 Accepted: 14 Mar 2010 Address letter and request for reprint at: Dkt. Anil K. Philip, Assistant Professor in the Department of Medicine, School of Pharmacy, College of Pharmacy and Nursing, Nizwa University, Birkat Al Mouz, Nizwa- 616, Sultanate of Oman. E-mail: philip@unizwa.edu.om, philipanil23@yahoo.co.in

Philip AK, et al. OMJ. 25, 70-78 (2010); doi: 10.5001 / omj.2010.24 Colonial DrugDelivery Programs: A Review of Key and Novel Approaches Approaching Ulcerative Colitis. Although these drugs are absorbed from the large intestine, it is widely believed that their effectiveness is due to the use of matter. Colonization of the drug reaching the colon depends on the composition, size of the redistribution of weight and storage time. Foam and suppositories have been shown to be stored mainly in the rectum and sigmoid columns while enema solutions have a high dispensing capacity.7 Due to the high concentration of water in the colon, the content of the colonies is very noticeable and their interaction does not work, so the availability of many drugs in the absorption membrane. The human colon contains more than 400 different types of bacteria such as living floras, a population of up to 1010 bacteria per gram content of colonies. Among the reactions of these intestinal plants are azoreduction and enzymatic cleavage i.e. glycosides.8 These metabolic processes can be involved in the conversion of many drugs and can also be used in the colon-directed delivery of insulin-like macromolecule peptides by oral administration. .

**Table 1**: Colon targeting diseases, drugs and sites.

| Target sites | Disease conditions | Drugs 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 To prevent first pass metabolism of orally ingested drugs | NSAIDS Steroids |
| | Oral delivery of peptides Oral delivery of vaccines | Insulin Typhoid |

**Target sites, colonic disease conditions, and drugs used for treatment are shown in Table 1.9**

**Advantages of CDDS over Conventional Drug Delivery**

Chronic colitis, i.e. ulcerative colitis, and Crohn's disease are currently treated with glucocorticoids, and other antiinflammatory drugs. 10 Administration of glucocorticoids i.e.dexamethasone and methyl prednisolone via oral and intravenous radiation produces systemic adverse effects including adenosuppression, immunosuppression, cushinoid symptoms, and resorption .11 and reduce the side effects of the system caused by high doses.

**Criteria for Selection of Drug for CDDS:-**

The best candidates for CDDS are drugs that show minimal absorption from the stomach or intestines including peptides. Drugs used to treat IBD, ulcerative colitis, diarrhea, and colon cancer are the most suitable for local colon delivery.13 CDDS treatment options are summarized in Table 2. Drug carrier is another contributing factor to CDDS. The choice of the carrier of certain drugs depends on the physical condition of the body and the disease in which the system will be used. Factors such as the chemical nature, stability and variability of the drug balance and the type of suction enhancement selected affect the carrier's choice. In addition, the choice of drug carrier depends on the active groups of the drug molecule.17 For example, aniline or nitro groups in a drug can be used to link us to another benzene group with an azo bond. Carriers, which contain additives such as polymers (can be used as matrices and hydro gels or coating agents) can affect the production and performance structures of systems.

**Approaches used for Site Specific Drug Delivery to Colon (CDDS)**

**Several approaches are used for site-specific drug delivery. Among the primary approaches for CDDS, These include:-**

**1) Primary Approaches for CDDS**

a) pH Sensitive Polymer Coated Drug Delivery to the Colon In the stomach, the pH is between 1 and 2 during fasting but increases after meals. From ileum to colon, pH drops dramatically. It is about 6.4 in cecum. However, pH values as low as 5.7 are estimated in the ascending colon for healthy volunteers.20 The pH in the flexible colon is 6.6 and 7.0 in the descending colon. The use of pH-based polymers is based on these differences in pH levels. Polymers defined as pH dependent on the delivery of certain colonic drugs are not solved at low pH levels but are gradually dissolving as the pH increases. the lower intestines, and the specifics of the site of the lesion may be poor. an ascending colony can also lead to incorrect site specifications for the construction of a single embedded unit.

**b) Delayed (Time Controlled Release System) Release Drug Delivery to Colon**

Time controlled system (TCRS) such as a sustainable or 72 Oman Medical Journal 2010, Volume 25, Issue 2, April 2010 delayed release rate forms are also the most promising programs for drug delivery. However, due to the wide range of possible abortions of dosage for volume forms in humans, in these methods, the timing of the arrival of column dosage forms cannot be accurately predicted, leading to inaccurate colonization. forms by extending the remaining time to about 5 to 6 h. However, the disadvantages of this system are:

- i) The duration of an abortion varies significantly between subjects or in a way that depends on the type and amount of food eaten.
- ii) Bowel movements, especially peristalsis or abdominal cramps can lead to changes in the bowel movement.24
- iii) Emergency mobility in different parts of the colon has been observed in patients with IBD, carcinoid syndrome and diarrhea, and ulcerative colitis. 9, 25,26 Therefore, time-based programs are not good for bringing drugs to the colony especially in the treatment of colon-related diseases. Proper integration of sensitive pH functions and release time into a single measurement form can improve site specification

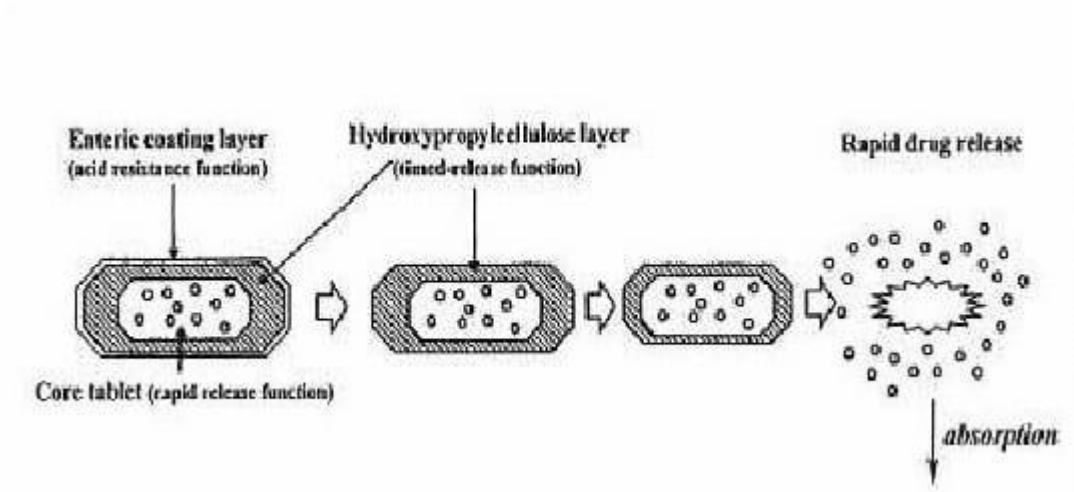


**Figure 1**: Design of enteric coated timed-release press coated tablet (ETP Tablet)

**C) Microbially Triggered Drug Delivery to Colon:-**

The colon microflora is in the range of 1011 -1012 CFU / mL, which contains mainly anaerobic bacteria, e.g. bacteroides, bifidobacteria, eubacteria, clostridia, enterococci, enterobacteria and ruminococcus etc. 25 This large microflora fulfills its energy needs by digesting a variety of nutrients left undigested in the small intestine, e.g. di- and tri-saccharides, polysaccharides etc. 29,30 In this fermentation, the microflora produces large amounts of enzymes such as glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase.31 Due to the presence of only decaying enzymes in the colon, the use of decaying polymers for the delivery of certain drugs to the colon appears to be a specific approach to the specific site of drug delivery to the colon. As the travel time of the measuring forms in the small intestine is less variable i.e. approximately 3 ± 1 hr. 27 The timing function (or timer function) should work better in the small intestine compared to the stomach. A small load of intestinal drugs will be delivered to the target side, and the withdrawal of the drug will begin within the prescribed time after the abortion. On the other hand, in the stomach, the release of the drug should be suppressed by the pH (acid resistance) sensory function in the dosage form, which will reduce the variability during stay in the stomach. , composed of three components, core tablet (fast extraction function), hydrophobic polymer layer filling (Hydroxy propyl cellulose layer (HPC), extraction function) and enteric coating (acid-resistant function) .23, 28 The tablet does not expel the drug from the stomach due to the acid resistance of the outer outer layer. After removal

from the stomach, the enteric layer dissolves rapidly and the intestinal fluid begins to slowly damage the polymer coated layer (HPC).

**Prodrug Approach for Drug Delivery to Colon:-**

Prodrug is derived from an inactive drug molecule of the parent drug that requires automatic or enzymatic modification in vivo to extract the active drug. With the delivery of the colonies, the prodrug was designed to undergo minor hydrolysis in the upper GIT leaflets, and obtained enzymatic hydrolysis in the colon by extracting an active drug from the drug administrator. Metabolism of compounds of azo by the bacteria in the gut is one of the most important. 73 Oman Medical Journal 2010, Volume 25, Issue 2, April 2010 studied the process of metabolic metabolism.38 Many other links involved in bacterial hydrolysis especially in the colon were repaired when the drug adhered to hydrophobic compounds such as amino acids, glucoronic acid, glucose, glactose, cellulose etc**.**

**i) Azo-Polymeric Prodrugs :-**

The new methods are aimed at the use of polymers as carriers of drug delivery to the colon. Both synthetic and natural synthetic polymers have been used for this purpose. Low-performance polymers have been used to form a polymer prodrug by azoza between the polymer and the drug moiety.48 This was assessed by CDDS. Various polymers have also been used as their composition depends on the active group found in the field of chemical bonding. In addition, prodrugs are new chemical substances, and require extensive testing before they can be used as carriers.39 The number of prodrugs has been described in Table 3.

| Carriers | Drug investigated | Linkage hydrolyzed | In vitro/in vivo model used | Performance of the Prodrug/conjugates |
|---|---|---|---|---|
| Azo conjugates Suphapyridine (SP) 5-ASA | 5-ASA | Azo linkage | Human | Site specific with a lot of side effects40 associated with SP |
| | 5-ASA | Azo linkage | Human | Delivers 2 molecules of 5-ASA as compared to suphasalazine |
| Amino acid conjugates glycine | Salicylic acid | Amide linkage | Rabbit | Absorbed from upper GIT, though metabolized by microflora of large intestine |
| Tyrosine/methionine | Salicylic acid | Amide linkage | Rabbit | Absorbed from upper GIT, though metabolized by microflora of large intestine |
| L – Alanin/DAlanine | Salicylic acid | Amide linkage | In vitro | Salicylic acid-l-alanine was hydrolysed to salicylic acid by intestinal microorganism but salicylic acid-D-alanine showed negligible hydrolysis thereby showing enantiospecific hydrolysis |

tested as a coating material over drug material. These have been found to be similarly affected by azoreducatase rupture in the large intestine. The discovery of peptide tablets containing polymer crosses linked to the azoaromatic group was found to protect the drug from digestion in the stomach and intestines. In the colon, the binding of azo decreases, and the drug is released. 28 The number of azopolymeric prodrugs described in Table 4.

**Table 4 :** Some azo polymer-based drug delivery systems evaluated for colon-specific drug delivery with summary of results obtained.

| **Azo polymers** | **Dosage from prepared** | **Drug investigated** | **In-vitro/ in-vivo model used** | **Summary of the results obtained** |
|---|---|---|---|---|
| Copolymers of styrene with 2-hydroxyethyl mrthacrylate | Coating over capsules | Vasopressin insulin | Rats dogs | These capsules showed biological respones characteristics of these peptide hormones in dog though it varied quantitatively |
| Hydrogels prepared by copolymerization of 2-hydroxyethy1 methacrylate with 4-methacryloyloxy) azobenzene | Hydrogen | 5-fluorouracil | In vitro | Drug release was faster and greater in human fecal media compared to simulated gastric and intestinal fluids |
| Segmented polynurethanes | Coating over pellets | Budesonide | Rat | These azopolymer-coated pellets were useful for colon-specific delivery of budesonide to bring healing in induced colites |
| Aromatic azo bond containing urethane analogues | Degradable films | 5-ASA | In vitro degradation of films in presence of lactobacillus | These films were degraded by azoreductase. The permeability of 5-ASA from lactobacillus treated films was significantly higher than that of control5 |

## 2. Newly Developed Approaches for CDDS

### a. Pressure Controlled Drug-Delivery Systems

As a result of peristalsis, higher pressures converge on the colon than in the lower abdomen. Takaya et al. improved pressure conveyed by colon delivery pills prepared using ethylcellulose, insoluble in water.62 In those systems, drug release occurs after the dissolution of a water-soluble pill due to pressure in the light of the colon. The thickness of the ethylcellulose membrane is the most important factor in the dispersion of the structure.63,64 The system also appears to depend on the size of the capsule and the size

### b. Novel Colon Targeted Delivery System (CODESTM)

CODESTM is a unique CDDS technology designed to avoid environmental problems associated with pH or time-dependent

systems.66,67 CODESTM is an integrated approach to CDH dependent and caused by microbes. It is made using a unique method that includes lactulose, which acts as a starting point for the release of certain drugs from the site to the colon, (Fig. 2). The system contains a traditional tablet component containing lactulose, which is further composed of acid-soluble substances, Eudragit E, and then coated with an enteric material, Eudragit L. The technical basis is that enteric coating protects the tablet while it is in the stomach and dissolves rapidly. following discharge from the abdomen.

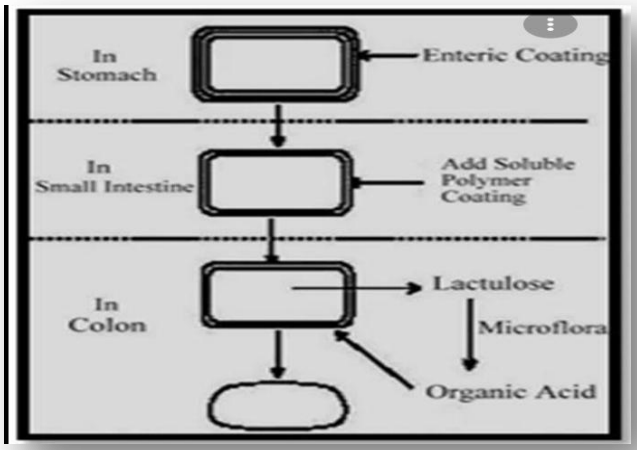


Figure 2: Schematics of the conceptual design of CODES

**c. Osmotic Controlled Drug Delivery (ORDS-CT)**

OROS-CT (Alza corporation) can be used to identify a local drug in the colon for the treatment of diseases or to achieve systemic absorption that cannot be otherwise achieved.70 The OROSCT system can be a single osmotic unit or can include as many as 5-6 units of inhalation, each 4 mm in diameter, enclosed within a solid gelatin pill, (Fig. 3) .71 Each bilayer suction unit contains a layer of osmotic push and a layer of drugs, both of which are surrounded by a non-abrasive membrane. The orifice is pierced in the membrane next to the drug layer. Immediately after the swallowing of OROSCT, the gelatin capsule containing push-pull units dissolves. Due to its impermeable coating of the drug, each suction unit is restricted from absorbing water into the abdominal aicous area, so no medication is delivered. As the unit penetrates the small intestine, the coating dissolves at a higher pH (pH> 7), water enters the unit, causing inflammation of the osmotic chamber, and at the same time creates a flowing gel in the drug chamber. Inflammation of the osmotic pressure chamber forces the drug gel out of the orifice at a rate that is precisely controlled by the rate of fluid flow through the immeasurable membrane.

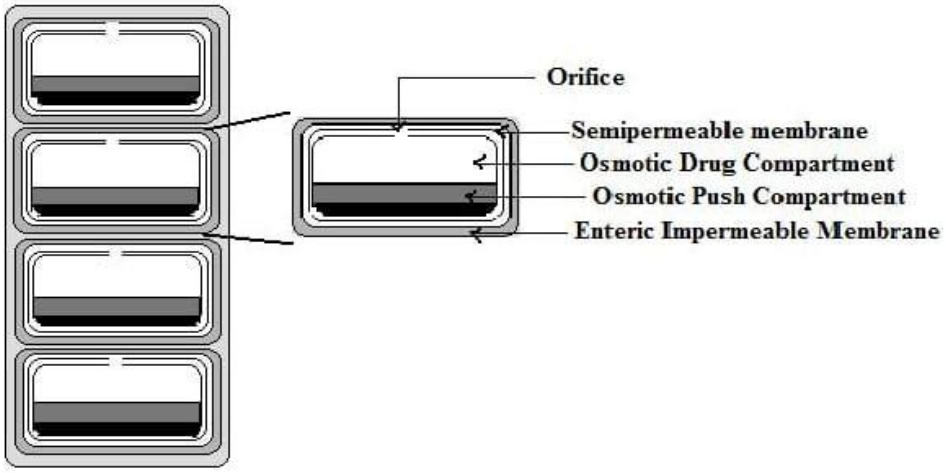


**Figure 3**: Cross-Section of the OROS-CT colon targeted drug delivery system

**In vitro dissolution test**

Reducing the regulation of the controls used for colonspecific drug delivery is often complex, and the reduction methods described in the USP cannot fully adapt to vivo conditions such as those related to pH, bacterial environment and mixing power.69 standard basket method. The same dispersion studies in different buffers can be performed to show the construction performance at different pH levels. Examination of colonspecific formation in various media comparing pH conditions and times that may be encountered at various locations in the gastrointestinal tract has been studied.76 Selected media, for example, pH 1.2 for myocardial infarction, pH 6.8 mimic region and small intestinal tract, -pH 7.2 mimic part of ileum. CDDS embedded tablets were investigated in a gradient termination study in three buffers. Capsules were tested for two hours at pH 1.2, and one hour at pH 6.8, finally at pH 7.4.77

**In vitro enzymatic tests**

Combine a system of carrier drugs in a fermenter that contains a suitable location for bacteria (strectococcus faccium and B.Ovatus). The amount of drug released at different times is determined. Drug release studies are performed on a buffer medium containing enzymes (ezypectinase, dextranase), or rat or guinea pig or rabbit content. The amount of drug released at a given time is determined, which is directly proportional to the degree of degradation of the polymer load.

**Drug Delivery Index (DDI) and Clinical Evaluation of ColonSpecific Drug Delivery Systems**

DDI is a calculated pharmacokinetic parameter, which follows one or more doses of oral prodrugs. DDI is the average dose of RCE (drug-related colonic exposure) to RSC (drug-related amount in the blood i.e. that is a systemic drug exposure). Higher DDI drug levels indicate better drug delivery. Colon intake of the drug was assessed by colonoscopy and intubation. Currently, gamma scintigraphy and high frequency capsules are the most popular methods used to evaluate colon delivery drug delivery systems.

**Conclusion:-**

The colonial region of GIT has become an extremely important center for drug delivery and absorption. CDDS offers significant therapeutic benefits to patients through local and systemic treatment. Colon specification may have been achieved through the delivery of Colon's targeted drugs ... Philip et al. 77 Oman Medical Journal 2010, Volume 25, Issue 2, April 2010 programs using natural materials that have been damaged by bacterial enzymes. Given the complexity of colonial drug delivery systems, as well as the uncertainty of current dissemination methods in finding possible in vitro / in-vivo combinations, challenges remain for pharmacologists to develop and validate a termination method that incorporates colonic physiological features, and yet can be commonly used in CD-field testing.

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