

## Approaches for Targeted Drug Delivery to Colon

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### ABSTRACT

The conventional drug delivery system for colonic disease may leads to absorption of drug across biological membrane of gastrointestinal tract (GIT). The absorption of drug throughout GIT may leads to increase in dose and associated side effects. Colon targeted drug delivery (CTDD) is a method of delivering medication to a patient in a manner that increases concentration of the medication in colon relative to other part of GIT. The aim of CTDD is to prolong, localize, target and have protected drug interaction to diseased tissue. The present review deals with primary as well as recent approaches of delivery of drug to colon.

**Key words:** Colon targeting, Colon targeted drug delivery, Targeted drug delivery, Drug delivery, colon.

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### INTRODUCTION

The aim of targeted drug delivery (TDD) is selective and effective localization of drug into the target at therapeutic concentrations with limited or no access to non-target sites. A targeted drug delivery system is chosen in drugs having instability, low solubility, short half-life, large volume of distribution, poor absorption, low specificity and low therapeutic index<sup>1,2</sup>. TDD may provide maximum therapeutic activity by preventing degradation or inactivation of drug during transit to the target site. It can also minimize adverse effects because of inappropriate disposition and minimize toxicity of potent drugs by reducing dose. The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiasis, colon cancer and local treatment of colonic pathologies<sup>3,4</sup>. The colon specific drug delivery system (CDDS) can be used for systemic delivery of protein and peptide drugs. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects<sup>5</sup>.

Primary Approaches for Colon targeted drug delivery: Primary approaches that are used for colon targeted drug delivery (CTDD) are as follow

pH Sensitive Polymer Coated Drug Delivery: The pH Sensitive polymer coated drug delivery to colon can be achieved as the pH along the gastrointestinal tract (GIT) varies as shown in table 1. This can be accomplished by means of coating that are intact at lower pH of the stomach but that will dissolved at neutral pH of the colon. These polymer used for coating should be resistant to the acidic condition of the stomach but ionize and get dissolved above a certain threshold alkaline pH found in small intestine. Thus it is possible to apply same concept to deliver drugs to the terminal of ileum or colon by use of

enteric polymers with a relatively high threshold pH for dissolution and subsequent drug release. The most frequently used polymer for this purpose is methacrylic acid and methylmethacrylate that dissolve at pH 6 (Eudragit L) and pH 7 (Eudragit S) have been investigated. But the pH of the distal is 6. This delivery system thus has a inclination to release the drug load prior to reaching the colon. To overcome the problem of premature drug release, a copolymer of methacrylic acid, methyl methacrylate and ethyl acrylate (Eudragit FS) which dissolve at slower rate and at higher threshold pH 7 to 7.5 was reported. One must question the impact of gastrointestinal disease on targeting performance since patient with ulcerative colitis are known to have markedly low colon pH<sup>6,7,8</sup>. Polymer used in pH Sensitive Polymer Coated Drug Delivery is shown in Table 1.

Time dependent drug delivery: In this approach, drug release to colon from the system after a predetermined lag time. The normal transit time in the stomach is 2 hr. which may vary, while in the small intestine it is relatively constant around 3hr. For the colon targeted drug release the lag time should similar to the time taken for the system to reach the colon. The lag time of 5 hr. is considered sufficient on the basis of relatively constant transit time in the small intestine (3hr). The lag time rely upon the gastric motility and size of the dosage form. One of the most primitive methods is the Pulsincap device. This device consists of a non-disintegrating half capsule body sealed at the open end with a hydrogel plug, which is enclosed by a water-soluble cap. The whole unit is coated with an enteric polymer to avoid the difficult of variable gastric emptying. When the capsule pass in the small intestine, the enteric coating dissolves and the hydrogel plug starts to swell. The quantity of hydrogel is adjusted so that it pops out only after the specified period of time to release the contents. In another approach, organic acids are filled into the body of

Table-1 Polymer and their threshold pH for CTDD

Polymer	Threshold pH
Eudragit® L 100-55	5.5
Eudragit® L-30D	5.6
Eudragit® L 100	6.0
Eudragit® FS 30D	6.8
Eudragit® S 100	7.0
Hydroxypropyl Methylcellulose Phthalate	4.5
Polyvinyl Acetate Phthalate	5.0
Hydroxypropyl Methylcellulose Phthalate 50	5.2
Cellulose Acetate Trimellate	5.0
Hydroxypropyl Methylcellulose Phthalate 55	5.4

a hard gelatin capsule along with drug substance as a pH-adjusting agent. The joint of the capsule is sealed using an ethanolic solution of ethylcellulose. The capsule is first coated with an acid soluble cationic polymer, then with a hydrophilic polymer hydroxyl propyl methylcellulose and finally enterically coated with hydroxy propyl methyl cellulose acetate succinate. After ingestion of the capsule, the outermost enteric layer of the coating prevents drug release in the stomach. The enteric layer and the hydrophilic layers dissolve rapidly after gastric emptying and water starts entering the capsule. When the environmental pH inside the capsule decreases by the dissolution of organic acid<sup>9,10,11,12</sup>.

**Microbially Triggered Drug Delivery:** The microflora of the colon is in the range of  $10^{11}$ - $10^{12}$  CFU/mL, containing mainly of anaerobic bacteria, e.g. bacteroides, bifidobacteria, eubacteria, clostridia, enterococci, enterobacteria and ruminococcus etc. This huge microflora fulfills its energy needs by fermenting numerous types of substrates that have been left undigested in the small intestine, e.g. disaccharides, trisaccharides and polysaccharides etc. For this fermentation, the microflora produces a vast number of enzymes like glucuronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azoreductase, 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. The varieties of enzymes, mainly of bacterial origin present in the colon, are essential for the biotransformation of the prodrugs<sup>13,14</sup>.

Microbially triggered drug delivery involve prodrug approaches of drug delivery and polysaccharide based drug delivery.

#### *Prodrug Approach for Drug Delivery*

Prodrug is a pharmacologically inactive derivative of a parent drug molecule that needs spontaneous or enzymatic transformation in vivo to release the active drug. A number of linkages susceptible to bacterial hydrolysis especially in the colon have been prepared where the drug is attached to hydrophobic moieties like azo linkage, amino acids, glucuronic acids, glucose, galactose, cellulose etc<sup>15</sup>.

Metabolism of azo compounds by intestinal bacteria is one of the most extensively studied bacterial metabolic process<sup>16</sup>.

Cyclodextrins conjugate of drug can be a versatile means of constructing prodrug for colon targeting. Prodrugs of Ibuprofen with  $\alpha$ ,  $\beta$  and  $\gamma$ -Cyclodextrins had been investigated for CTDD. Prodrugs of methotrexate with  $\alpha$  and  $\beta$ -Cyclodextrins were also synthesized for CTDD. The dose of methotrexate gets reduced by 12 fold and ulcerogenic potential of free drug were also masked<sup>17</sup>. Glucuronide and sulphate conjugation may leads to inactivation of drug. Bacteria present in lower gastrointestinal tract secrete glucuronidase that glucouronidate a variety of drugs in the intestine. As glucuronidation leads to release of active drug and enables its reabsorption, glucuronide prodrugs would be useful in CTDD<sup>18</sup>.

Non-essential amino acids such as glycine, tyrosine, methionine and glutamic acid conjugate with salicylic acid and these conjugates show more enzymatic specificity for hydrolysis by colonic enzymes leading to the minimal absorption and degradation in the upper GIT<sup>19</sup>.

Drawbacks of the prodrug approach is that it is not applicable to all types of drug depends upon the functional group available on the drug moiety for chemical linkage.

#### *Polysaccharide based drug delivery*

These polymers protect the drug from the surroundings of stomach and small intestine, and are capable 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<sup>20</sup>.

Recent approaches for CTDD: Primary as well as recent approaches of CTDD is shown in Figure 1. The recent approaches of CTDD is as follow

**CODES™ technology:** CODES™ is a distinctive CDDS technology that was designed to avoid the intrinsic difficulties associated with pH or time dependent systems. CODES™ is a collective approach of pH dependent and microbially triggered CDDS. It has been developed by applying a unique mechanism involving lactulose, which acts as a trigger for site specific drug release in the colon. One typical configuration of CODES™ comprises of a core tablet coated with three layers of polymer coatings. The outer coating is composed of a standard enteric polymer such as Eudragit® L. Once the unit passes through the pyloric and into the duodenum, this coating

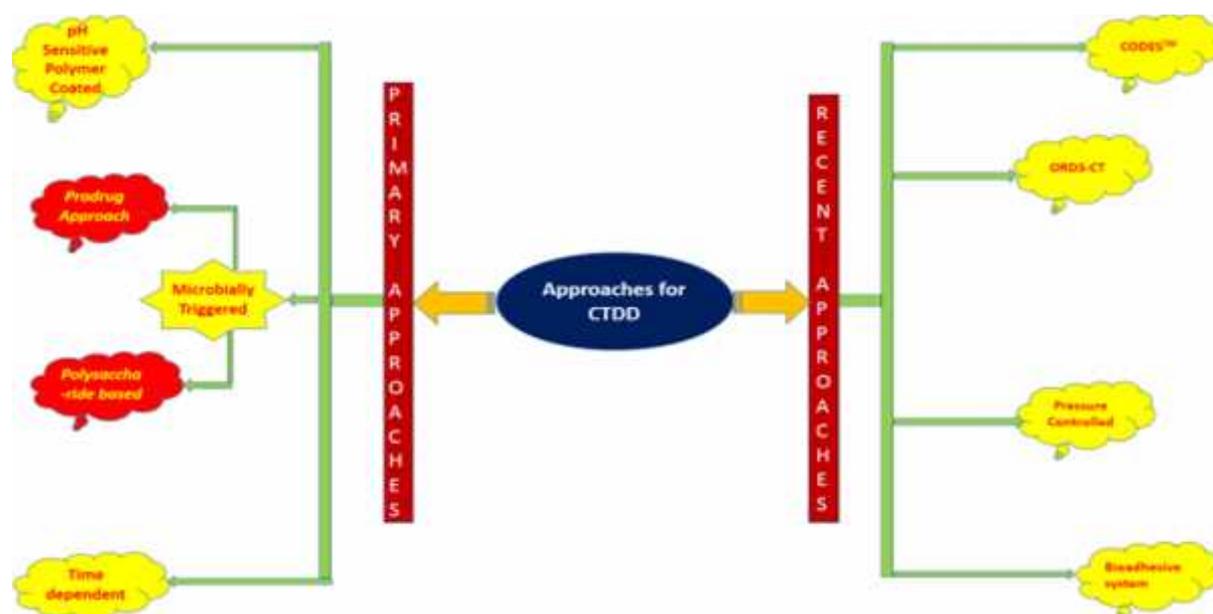


Figure 1 Approaches of CTDD

dissolves exposing the undercoating, which is composed of Eudragit® E. This coating will not dissolve in the environment of the small or large intestine. The undercoating permits lactulose to be released into the environment adjacent to the tablet. This disaccharide is then metabolized to short chain fatty acids that lower the local pH to the point where the Eudragit E dissolves. This final dissolution step exposes the core of the tablet allowing drug dissolution to occur<sup>21,22</sup>.

Osmotic controlled drug delivery (ORDS-CT): The OROS-CT is used to target the drug to the colon that is otherwise unattainable. The OROS-CT system can be single osmotic unit or may integrate as many as 5-6 push-pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule (Figure 3). Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semi permeable membrane. An orifice is pierced through the membrane next to the drug layer. Instantly 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 ( $\text{pH} > 7$ ), water enters the unit, causing the osmotic push compartment to swell and alongside creates a flowable gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semipermeable membrane. For treating ulcerative colitis, each push pull unit is designed with a 3-4 hour post gastric delay to prevent drug delivery in the small intestine. Drug release begins when the unit reaches the colon. OROS-CT units can maintain a constant release rate for up to 24 h in the colon<sup>23</sup>.

Pressure Controlled Drug-Delivery Systems: This approach depends on the strong peristaltic waves in the colon that lead to a momentarily increased luminal

pressure. The release of drug occurs following disintegration of water soluble polymer capsule as a result of pressure in the lumen of colon<sup>24</sup>.

Bio adhesive system: This method has been created upon principle of adhesion between drug and the biological membrane by the virtue of which the drug molecule remains in contact with particular organ for an increased period of time. It leads to extended residence time of the drug molecule it tends to high local concentration. This approach can be applied to colon target delivery system. Various polymers employed for bio adhesive system are polycarbophils, polyurethanes, polyethylene oxide and polypropylene oxide<sup>25</sup>.

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