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REVIEW ON: RACENT APPROACH TO COLON AS TARGATED DRUG DELIVERY SYSTEN IN FUTURE

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ABSTRACT

Colon is targated for colon associated disease Like Chron's disease, Inflammatory bowel disease, Colon cancer, Ulcerative colitis and also for the delivery site for systemic delivery of drugs like antihypertensive, Antihistaminic. Colon target is more specific those drug which is inactive at upper part of GIT. To achive maximum site specific when two or more approaches are prefferd on single approaches like Time dependent, Osmotic controlled, Prodrug approach, pH controlled system are very effective. Major goal for colon as targated system to achive effective concentration of drug release in systemic circulation and hence increase bioavailability.

KEYWORDS: CDDS, GIT, Protein.

INTRODUCTION

The goal of any delivery system is to provide a therapeutic amount of drug to a proper site in the body so that the desired concentration can be achieved prompting and then maintained.[1] Oral administration of different dosage forms is the most common form of administration due to greater patient compliance and flexibility.[2] The colon is a site where both local and systemic delivery of drug can take place.[3] Colon targeted drug delivery would ensure direct treatment, lower dosing and least systemic side effect.[4] They are the better choice for chrons disease, celiac disease, ulcerative colitis and in the detection of GIT bleeding[5] and their systemic absorption of protein and peptide.[6]

The pH of the gastrointestinal tract gradually increases as one move down the gastrointestinal tract from the stomach (pH-1. 5-3) to the terminal ileum (pH-7-8).[7] The important bacteria present in the colon such as Bacteroides, Bifidobacterium, Eubacterium, peptococcus, Lactobacillus clostridium, secreate a wide range of reductive and hydrolytic enzyme such as β-galacctosidase, nitroreductase, azoreductase, deaminase and urea hydroxylase.[8]

The colon is belived to be a suitable absorption site for peptide and protein drugs for the following reasons (i) less diversity and intensity of digestive enzyme (ii) comparative proteolytic activity of colon mucosa is much less than that observed in small intestine, thus CDDS proteins, peptide drugs from hydrolysis and enzymeticdegredation in duodenum and jejanum and eventually release the drug into ileum or colon which leads to greater bioavailability.[9]

Advantages of colon targeting drug delivery system over conventional drug delivery[10]

Colon is an ideal site for the delivery of agents to cure the local diseases of the colon.

- Local treatment has the advantage of requiring smaller drug quantities.
- Reduces dosage frequency. Hence, lower cost of expensive drugs.
- Possibly leading to a reduced incidence of side effects and drug interactions.
- The colon is an attractive site where poorly absorbed drug molecules may have an improved bioavailability.
- Reduce gastric irritation caused by many drugs.
- Bypass initial first pass metabolism.
- Improve patient compliance.
- Targeted drug delivery system.
- It has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.
- It has low hostile environment, less peptidase activity so peptides, oral vaccines, insulin, growth hormones, can be given through this route.

Approaches used for site specific drug delivery to colon (CDDS)[10]

Several approaches are used for site specific drug delivery, In general there are five approaches for colon targeted delivery namely,

1. pH dependent system
2. Delayed or Time dependent systems
3. pressure dependent systems
4. Prodrug approach system
5. Polysaccharides based approach
6. Novel approach.

Pulsicap

- CODES-Novel Colon Targeted Delivery System
- OROS system.

(1) pH Dependent System

Methylic acid copolymer such as Eudragit L-100 and Eudragit S-100 commonly been used as pH dependent polymer for coating solid dosage forms (because of their solubility at pH 6or higher and 7 respectively, which is considered as the suitable pH for Colon Targated delivery.[13]

Eudragit S -100 based microsphere were prepared by oil-in-oil solvent evaporation method using different drug polymer ratio (1:1, to 1:5)stirring speed (1400rpm)and emulsifying concentration (0. 5%-1. 5%w/v)and all formulation were evaluated for particle size and shape, swellability were high for all eudragit microsphere. The yield of preparation and encapsulation effeciencies were high for all eudragit microsphere.[14]

Various Formulation were developed by using release rate controlling polymer like HPMC K4M, eudragit L-100, Ethylcellulose by direct compression method.[15]

(2) Relayed or time controlled release drug delivery System[11]

Time controlled drug delivery system include sustained or delayed release system. In this system the delayed release or colon targeted drug delivery is attained by prolonging the lag time. This transient time varies in different parts of gastrointestinal tract. This transient time is responsible for the delayed release of drug. The main drawback of this delivery system are that the transit time varies from one person to other and amount of food intake. It also varies with the peristalsis or contraction in the gastrointestinal tract.[11]

(3) Pressure dependent system

As a result of peristalsis higher pressure are encountered in the colon than in the small intestine. Pressure controlled colon delivery capsule prepare using an ethylcellulose, which is insoluble in water. In such system drug release occur 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. The system also appeared to depend on capsule size and density.[17]

In pressure controlled system gelatin capsule are coated with water insoluble polymer like ethylcellulose on their inner side. The drug is insoluble into the capsule along with suppository base. The thickness of ethylcellulose coating determine the disintegration capacity of the capsule. After administration the suppository base dissolve at body temperature, the water from intestional contents is absorbed resulting in increased viscocity which leads to an increase in the pressure in the capsule. The pressure in the capsule expels the drug into the colon. The intestinal pressure developed varies with the circadian rhythams, state of body, Food administration etc.[18]

(4) Prodrug approach

The main approach of microbial triggered drug delivery system is Prodrug. In this approach the drug release from the formulation is triggered bythe gut microflora. Prodrug is a pharmacologically inactive derivative of the parent molecule which requires enzymetic transformation in the biological environment for releasing the active drug at the targeted site. Prodrug are prepared by linkage of drug with hydrophobic moieties such as amino acids, glucuronic acid, glucose galactose, cellulose etc. In the presence of enzyme released by the microflora these prodrug molecules get hydrolysed.

Generally a prodrug is successful as acolon drug carrier if it is hydrophilic and bulky to minimize absorption from the upper GITand if once in the colon, it is converted into more lipophilic drug molecule, which is then available for the absorption.

Limitation of the prodrug approach is that is less versatile approach because its formulation depends upon the functional group presented on the drug moiety for chemical Linkage.[19]

Prodrugs evaluated for colon specific drug delivery with there in vitro/in vivo performance

Carrier	Drug investigated	Linkage hydrolyzed	In vitro/in vivo model used	Performance of the Prodrug/conjugates
Suphapyridine (SP) 5-ASA	5-ASA	Azo linkage	Human	Delivers two molecules of 5-ASA as compared to suphasalazine.
Amino acid conjugates glycine	Salicylic acid	Azo 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.
L – Alanin/D-Alanine	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 there by showing enantiospecific hydrolysis[32]
Glycine	5-SAS	Amide linkage	In -Vitro	Prodrug was stable in upper GIT and was hydrolysed by cecal content to release 5-ASA.[33]
Glucouronide conjugates glucuronic acid	Naloxone/ Namefen	Glucouronide linkage	Rat	When given to morphine dependent rats, these reversed the GIT side effects caused by morphine without causing CNS withdrawal symptom because of activation in large intestine followed by a resultant diarrheas.[34]

(5) Polysaccharides based approach

A large number polysaccharide such as amylase, Guar-gum, pectin, chitosan, Inulin, Cyclodextrins, Chondrin sulphate, Dextrans, dextrin, and Locust bean gum have been investigated for their use in colon targated drug delivery system.[12] Pectin is a predominately linear polymer of mainly α-(1-4)- linked to D-galacturonic acid residues interrupted by 1, 2-linked L-rhamnase residues. Pectin is a polysaccharide found in the cell walls of plants. The rationale for the development of a polysaccharidebased delivery system for colon is the ability of the colonic microflora to degrade various types of polysaccharides that escape small bowel digestion. Pectins are polysaccharides and consist of linear polymers of d-galacturonic acid residues with varying degrees of methyl ester substituents. The degree of esterification (DE) and degree of amidation (DA), which are both expressed as a percentage of carboxylgroups (esterified or amidated), are important means to classify pectin. It is totally degraded by colonic bacteria but is not digested in the upper GI tract.[16]

(6) Novel Approach[20]

Most recently new colon specific delivery system are developed. These are colon delivery capsule, CODESTM, osmotically drug delivery system, pulsicapsystem, time clock system etc.

Pressure controlled release system

Strong peristaltic waves in the colon occurs only three to four times a day but this result in the more luminal pressure within the colon as compare to pressure in small intestine, which forms the base for design of pressure-controlled systems. Inside, stomach and small intestine, contents are more fluidic in nature because of because of abundant water present in digestive juices, where as in colon, the viscosity get significantly increased due to reabsorption of water from the lumen and formation of feces38. This system consists of drug inside gelatin capsule coated with water insoluble polymer ethyl cellulose on their inner region. The drug is incorporated into the capsule along with suppository base (Dissolves at body temperature). The disintegration capacity of the capsule is the function of thickness of ethyl cellulose, administration of the capsules leads to dissolution of suppository base absorption of water from intestinal contents is resulted in increased viscosity which leads to an increase in the pressure in the capsule causing capsule to expel the drug into the colon.[3] The preferred thickness of the capsule wall is about 35- 60 μm.

Pulsatile drug delivery system

i. Pulsincap system

In this system swellable hydrogels are used to seal the drug contents inside capsule and When it comes in contact with the dissolution fluid, plug gets pushed off from the capsule and the drug will be released. Polymers of different grades of hydroxyl propyl methyl cellulose (HPMC), poly methyl methacrylate and polyvinyl acetate are used as hydrogel plugs. The lag time is the function of length and point of intersection of the plug, in the capsule body.

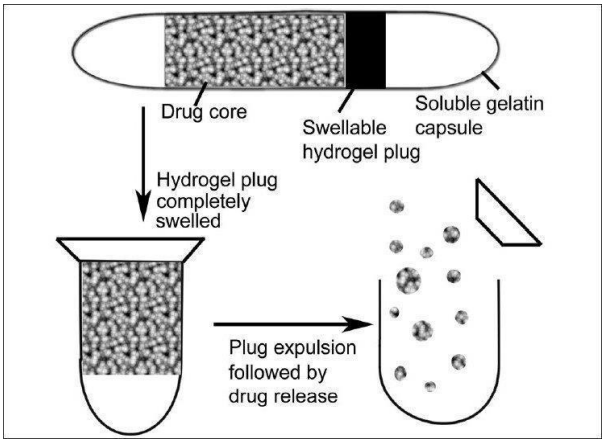

Figure 1: Pulsincap system.

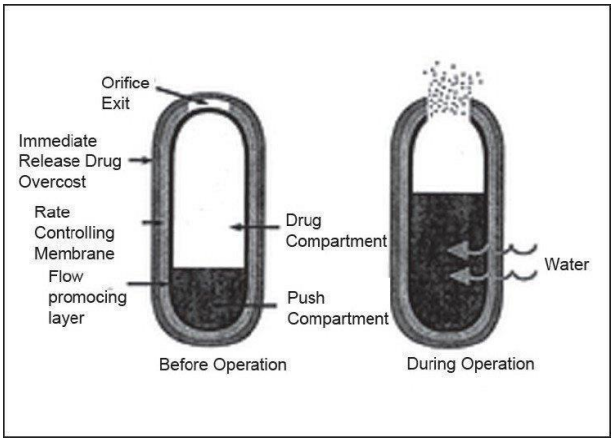

Figure 2: Control release system.

ii. Port system

In this system capsule body consists of an insoluble plug which contains osmotically active agent and drug formulation enclosed in a semipermeable membrane. As capsule comes in contact with the dissolution fluid, fluid movements occurs across the semipermeable membrane into the capsule due to which pressure inside the capsule get increased resulting into release of drug due to expelling of the plug.

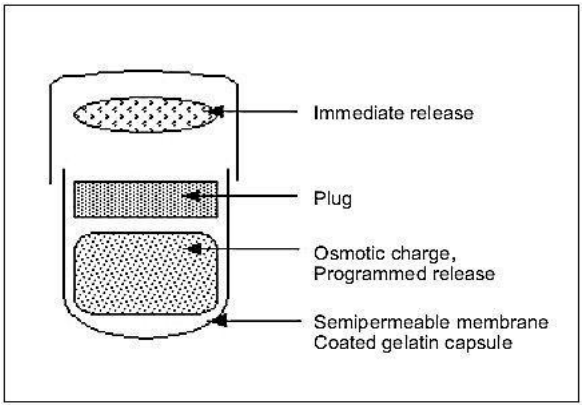

Figure 2: Port system release.

Osmotic controlled drug delivery system (ORDS-CT System)

The OROS-CT system is a single osmotic unit or 5-6 push-pull units, each of which is 4 mm in diameter, encapsulated within a hard gelatin capsule. Push pull units are bilayered having outer enteric impermeable membrane and inner semi permeable membrane having orifice from which drug diffuses out. During their way to through the GIT the enteric impermeable membrane prevents the water absorption into the unit. The outer impermeable enteric membrane dissolved as it reached to small intestine (pH>7). Water enters through the semi permeable membrane resulting into the swelling of push layer which forces the drug into the surrounding environment via orifice. These osmotic controlled drug delivery systems deliver the drug at a constant rate for up to 24 hr.

Novel Colon targeted delivery system (CODESTM)

CODESTM is a unique CDDS technology employs combined approach of pH dependent and microbially triggered CDDS. This system utilizes the enzymatic degradation of lactulose polysaccharide by colonic bacteria. The system involves the coating of tablet core that contain lactulose, by acid soluble material, Eudragit E, and then subsequently coated with an enteric material, Eudragit L. The enteric coating provides acid resistant in stomach and as it passes the stomach it get dissolved, Now acid soluble material coating provides resistant to basic pH of the small intestine. When it reaches to colon the bacteria enzymetically degrade the polysaccharide (lactulose) into organic acid that will result in lowering of the pH in the surrounding which is sufficient to affect the dissolution of the acid soluble coating and subsequent drug release.[21]

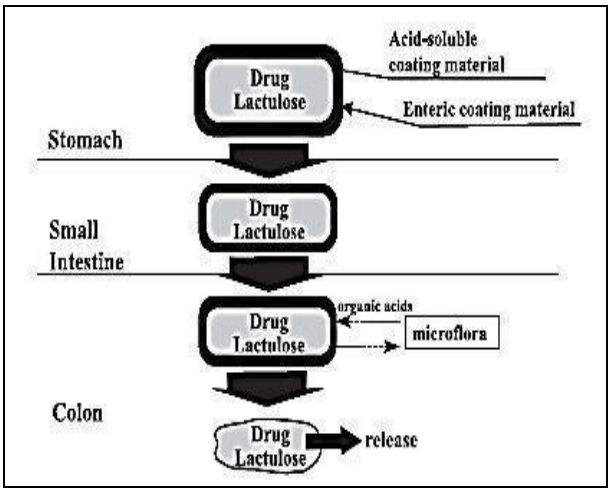

Figure 4: CODESTM delivery.

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