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Review Article

COLON TARGETED DRUG DELIVERY SYSTEM ADVANCE IN NOVEL DRUG DELIVERY SYSTEM

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Abstract

The oral route is considered to be the most preferred route for administration of drugs for systemic effect, but the oral route is not suitable to the administration of drug for lower gastrointestinal (GI) diseases, this happened due to their release at upper GI tract (stomach, small intestine), which further minimizes the accessibility of drugs at the lower GI tract. To overcome this difficulty, colon-specific drug delivery systems have been broadly analyzed during the last two decades. Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon (ulcerative colitis, Chron's disease, carcinomas and infections) whereby high local concentration can be achieved while minimizing side effects that occur because of release of drugs in the upper GIT or unnecessary systemic absorption. The simplest method for targeting of drugs to the colon is to obtain slower release rates or longer release periods by the application of thicker layers of conventional enteric coatings or extremely slow releasing matrices. Various pharmaceutical approaches to to colon targeted delivery system are a) covalent linkage of drug with carrier b) coating with polymers c) coating with pH sensitive polymers d) coating with biodegradable polymers.

Keywords: Colon targeting, site specificity, colonic diseases, biodegradable polymers

INTRODUCTION

A dosage form that delivers the drug into the colon rather than the upper GIT is called a colonic drug delivery system, and this delivery system has a number of advantages. The large intestine is attracting interest as a site where a poorly absorbed drug molecule may have improved bioavailability. This region of the large intestine is known to have a somewhat less hostile environment with less variety and intensity of activity than the stomach and small intestine. Oral administration of drugs to the colon is valuable in the treatment of colonic diseases (ulcerative colitis, Crohn's disease, cancers, and infections), whereby high local concentrations can be achieved while minimizing side effects that occur due to drug release in the upper GIT or unnecessary systemic absorption. The large intestine is rich in lymphoid tissue, the uptake of antigens into the mast cells of the colonic mucosa creates rapid local production of antibodies, which aids in effective vaccine delivery. The large intestine has a longer retention time and appears highly sensitive to agents that increase the absorption of a poorly absorbed drug. The simplest method for targeting drugs to the colon is to achieve a

slower release rate or a longer release period by applying thicker layers of conventional enteric coatings or extremely slow-release matrices.[1-6]

Colonic drug delivery is a relatively recent approach to the treatment of IBS, and recommended treatments include anti-inflammatory drugs, chemotherapy, and antibiotics that must be released in the colon. Such topical treatment has the advantage of requiring small amounts of drug, which can lead to a reduction in side effects and drug interactions. The usual treatment for inflammatory bowel disease is to take high-dose anti-inflammatory drugs frequently to induce remission of active disease, leading to side effects such as dizziness, GI disturbances, headaches, and skin rash. A colon-specific drug delivery system (CDDS) should be able to protect the drug en route to the colon, i.e. drug release and absorption should not occur in the stomach or small intestine, nor should the bioactive substance be degraded at either site dissolution. , but is released absorbed once the system reaches the large intestine. Colonic formulations are also suitable for the administration of drugs that are polar and/or susceptible to chemical and enzymatic degradation in the upper GIT; especially therapeutic proteins and peptides are suitable for colonic deliveries. Proteins and peptides such as insulin, calcitonin, and vasopressin can be delivered systemically through colonic absorption.

Advantages of colon targeted delivery system –

a. Delivery of drug in its intact form as close as possible target site.

b. The ability to cut the conventional dose

c. Reduced incidence of adverse side effects

d. Due to negligible activity of brush border membrane peptidase and less activity.

e. Low hostile environment, the colonic transit time is long 20 – 30hr and colonic tissue highly responsive to the action of absorption enhancers.

Criteria for Selection of Drug for CDDS

The best candidates for CDDS are drugs that show poor absorption from the stomach or intestine, including peptides. Drugs used in the treatment of IBD, ulcerative colitis, diarrhea, and colon cancer are ideal candidates for local delivery to the colon.[13] Drug selection criteria for CDDS are summarized.

Drug Carrier is another factor that affects CDDS. The choice of carrier for specific drugs depends on the physicochemical nature of the drug as well as the disease for which the system is to be used. Factors such as the chemical nature, stability and partition coefficient of the drug and the type of absorption enhancer chosen influence the choice of carrier. Furthermore, the choice of drug carrier depends on the functional groups of the drug molecule.[17] For example, aniline or nitro groups on a drug can be used to attach to another benzene group via an azo bond. Carriers that contain additives such as polymers (can be used as matrices and hydrogels or coating agents) can affect the release properties and efficacy of the systems.[13]

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, pH ranges between 1 and 2 during fasting but increases after eating.[21] The pH is about 6.5 in the proximal small intestine, and about 7.5 in the distal small intestine.[22] 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.[23]. The pH in the transverse colon is 6.6 and 7.0 in the descending colon. Use of pH dependent polymers is based Due to the difference in these pH values. Polymers in colon-

specific drug delivery, described as pH dependent, are insoluble at low pH but become more soluble with increasing pH.[25] Decreasing pH from the end of the small intestine into the colon is also a problem , which can lead to long lag times at the ileocecal junction, or rapid passage through the small intestine. Ascending colon may reduce site specificity of single-unit enteric-coated formulations.[24]

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

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.[26] The dosage forms may also be applicable as colon targeting dosage forms by prolonging the lag time of about 5 to 6 h.

2. **Newly Developed Approaches for CDDS**

a. Pressure Controlled Drug-Delivery Systems

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. developed pressure controlled colon-delivery capsules prepared using ethylcellulose, which is insoluble in water.[43] 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.[44,45] 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. 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.[46] Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to humans.

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

CODESTM is an unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems.[47,48] CODESTM 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.[49] 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 effect the dissolution of the acid soluble coating and subsequent drug release.[20]

CONCLUSION:

Colon targeted drug delivery system generate both local and systemic effects. The main advantage of colon drug delivery system is, long transit time, near neutral pH, reduced enzymatic activity and increased responsiveness to absorption enhancers. The main aim of CDDS is to preserve the formulation during its transit through the stomach and small intestine. There are some novel approaches more specific compared to primary approaches like pressure controlled drug delivery

system, pulsincap system, port system; colon-targeted delivery system (CODES), multiparticulate system and pro-biotic. Both polysaccharides and synthetic polymers are used for the colon targeting. The colon targeted drug delivery provides safe, effective and less expensive delivery of drugs with minimum fluctuation at the target site.

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