EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 6
448-453
Year: 2019

COLON TARGETED DRUG DELIVERY SYSTEM: A NOVEL APPROACH

Bhawna Mishra*, Ashiq Qureshi and Dr. Vineeth Chandy

India.

***Corresponding Author: Bhawna Mishra**
India.

Article Received on 09/04/2019 **Article Revised on 30/04/2019** **Article Accepted on 21/05/2019**

ABSTRACT
Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, etc. but also for the systemic delivery of proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs and anti-diabetic agents. To achieve successful colon targeted drug delivery, a drug need to be protected from degradation, release and absorption in the upper portion of the GI tract and then to be ensured abrupt or controlled release in the proximal colon. This review mainly compares the primary approaches for CDDS (Colon Specific Drug Delivery) namely prodrugs, pH and time dependent systems, and microbial triggered systems, Treatment could be more effective if it is possible for drug to be directly delivered to colon.

KEYWORDS: Crohn's disease, ulcerative colitis, etc.

1. INTRODUCTION

The oral route of drug administration is the most convenient and important method of administering drugs for systemic effect. Nearly 50% of the drug delivery systems available in the market are oral drug delivery system and these systems have more advantages due to patient acceptance and ease of administration.[1-2]

Formulations for colonic delivery are also suitable for delivery of drugs, which are polar and / or susceptible to chemical and enzymatic degradation in upper GIT; in particular, therapeutic proteins and peptides are suitable for colonic deliveries.[3-4] Proteins and peptides such as insulin, calcitonin and vasopressin may be delivered systematically via colonic absorption.

1.1 Therapeutic advantages of targeting drug to the diseased organ includes

- The ability to cut down the conventional dose.
- Reduced the incidence of adverse side effects
- Delivery of drug in its intact form as close as possible to the target sites.
- 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 (e.g. NSAIDS).
- Improve patient compliance.
- It has a longer retention time and appears highly responsive to agents that enhance absorption of poorly absorbed drugs.

1.2 Criteria for selection of drug for colonic drug delivery drug candidate

1.2.1 Drug candidate

Drugs which show poor absorption from the stomach as intestine including peptide are most suitable for CDDS. The drugs used in treatment of inflammatory bowel disease ulcerative colitis, diarrhea and Colon cancers are ideal candidates for local colon delivery.[12]

1.2.2 Drug carrier

The selection of carrier for particular drug candidate depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. The factors such as chemical nature, stability and partition coefficient of drug and the type of absorption enhancers chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of drug molecule. The carriers which contain additives like polymers (may be used as matrices and hydro gels as coating agents) may influence the release properties and efficacy of the systems.[13]

1.3 Factors to Be Affected In the Design of Colon - Targeted Drug Delivery System

1.3.1 **Physiological factors**

1.3.1.1 Gastric emptying

Drug delivery to the colon upon oral administration depends mainly on gastric emptying and bowel transit time. Upon reaching the colon the transit time of dosage form depends on the size of the particles. Smaller particles have more transit time compared to larger particles. Diarrhea patients have shorter transit time whereas constipation patients have longer transit times.

1.3.1.2 PH of colon

The pH of GIT varies between different individuals. The food intakes, diseased state, etc. influences the pH of the GIT. This change in the pH in different parts of GIT is the basis for the development of colon targeted drug delivery systems. Coating with different polymers is done to target the drug to the site.

2. Anatomical And Physiological Characteristics of the Colon

The large intestines extend from the ileocaecal junction to the anus which is divided into three main parts colon, rectum and anal canal. The colon constitutes caecum, ascending colon, hepatic flexture, transverse colon, splenic flexures, descending colon and sigmoid colon (Fig 1.1). The average size of colon is 1.5 m long, the transverse colon is the longest and most mobile part and has an average diameter of about 6.5 cm.[9]

2.1 Functions of colon[10]

1. It creates suitable environment for the growth of colonic microorganisms.
2. Fecal contents storage reservoir.

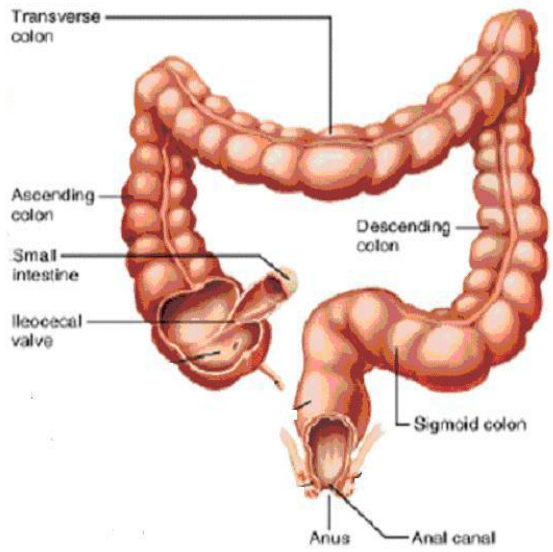


Fig 1: Ascending, transverse, descending and sigmoid colon.

2.2 Absorption of Drug from Colon

Studies in rat have revealed that paracellular absorption is constant through the small intestine, but transcellular absorption appears to be limited to the small intestine, with negligible colonic absorption by this route. The drugs stay in contact with mucosa in colon for a longer period than in small intestine which compensates the much lower surface areas of colon for absorption.

2.2.1 Factors Affecting Drug Absorption from Colon.[11]

The colon specific drug delivery primarily affected by two physiological factors, these are pH level and the transit time. The other factors which need to be considered are as follows 7.

- Physical characteristic of drug (pka, degree of ionization).
- Colonic residence time as detected by gastrointestinal tract motility,
- Degradation by bacterial enzymes and byproducts,
- Local physiological actions of drug,
- Disease state,
- Use of chemical absorption enhancers.

2.3 Colonic Diseases

2.3.1 Inflammatory bowel disease (IBD)

Inflammatory bowel disease (IBD) is the communal terms for a group of idiopathic intestinal conditions include ulcerative colitis (UC) and Crohn'sdisease (CD) (Fig 1.2). IBD is considered to be chronic relapsing disorder allied with uncontrolled inflammation within the gastrointestinal tract which may lead to the development of colorectal cancer later in life.

2.3.2 Crohn's disease

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract; it is characterized by a granulomatous inflammation affecting any part of the tract, normally form fistulae. The Crohn's disease was first described by the Crohn, Ginzburg, & Oppenheimer in 1932. Large intestine 20 to 30.

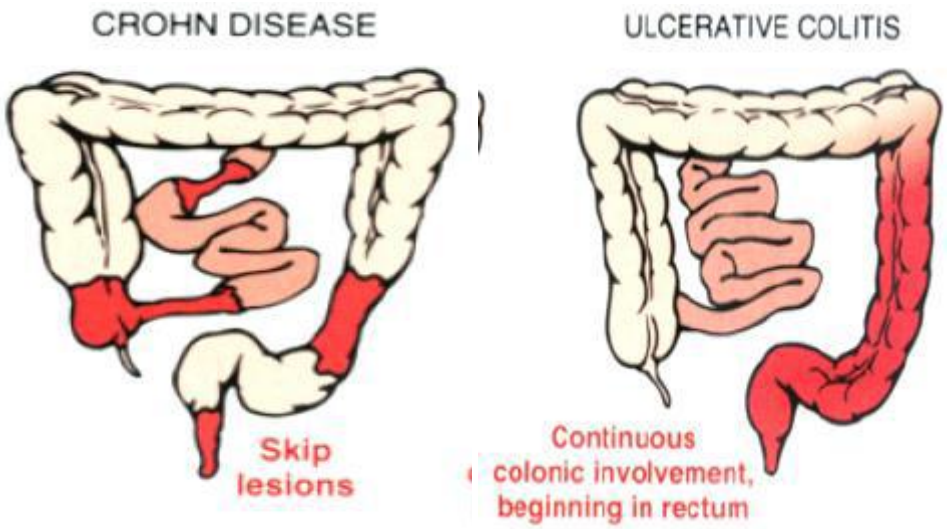


Fig 2: Locations of IBD in colon.

The reason of crohn's disease are not known but clearly involves interplay between genetic and environmental factors. The latter includes smoking and intestinal luminal factors.

2.3.3 Ulcerative colitis

It is a chronic inflammatory disorder of colon limited to the large intestines against the case with Crohn's Disease where any part of the alimentary tract may be involved. The condition usually manifests in the form of inflammation of the rectum extending further-up to colon. The inflammation may be limited to the left-hand side of the colon or extend1[10] to entire colon.

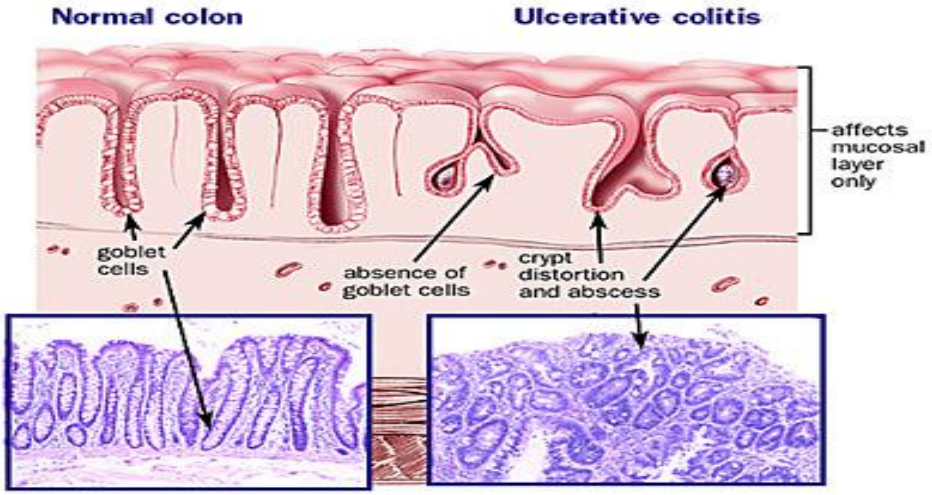
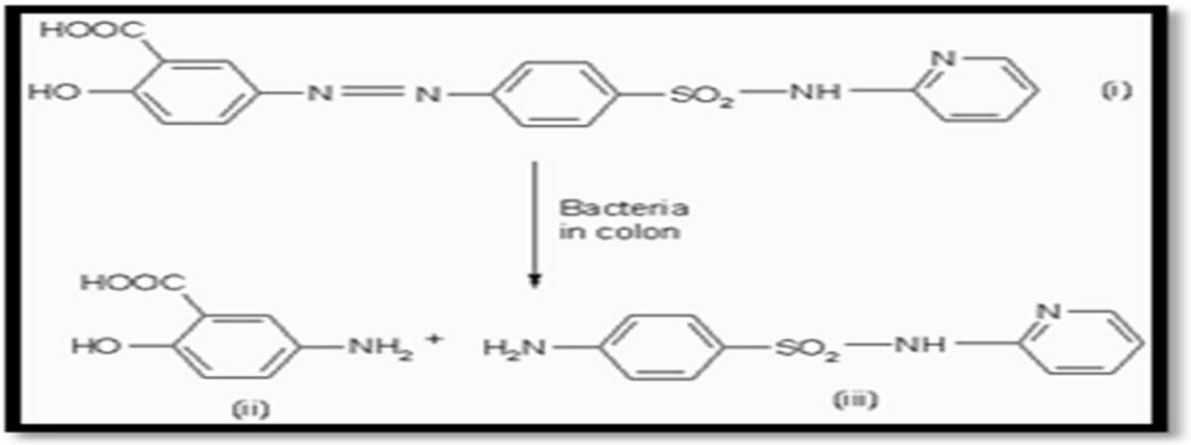


Fig 3: ulcerative colitis.

3. Approaches to Deliver Intact Molecule to Colon

3.1 Microbial Triggered Drug Delivery to Colon

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 et.[22] This vast micro flora 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 micro flora produces a vast number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase[25] 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.5 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.[26-27-28]



3.1.1Polysaccharide based delivery system

Polysaccharide based delivery system is the other form of microbial triggered drug delivery system. Naturally occurring polysaccharides like guar gum, xanthan gum, chitosan, alginates, etc. are used in targeting the drugdelivery. These are broken down by the colonic microflora to simple saccharides.[28]

3.1.2 Prodrug approaches

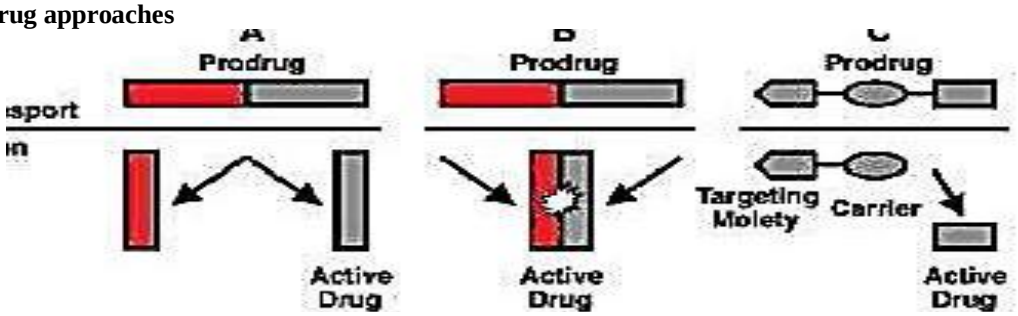
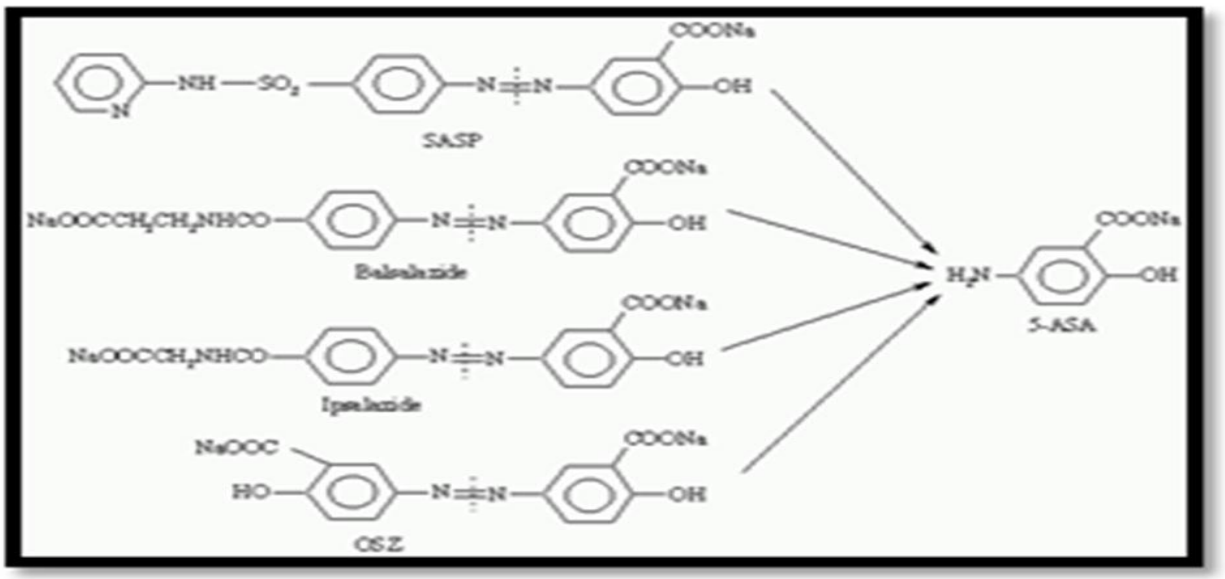


Fig 3: prodrug approaches for cdds.

3.1.2.1Azo bond conjugate

In this approach drug has been conjugated by azo bond. The azo bond is stable in the upper GIT and is cleaved in the colon by azoreductases produced by the microflora. These azo compounds are extensively metabolized by the intestinal bacteria, by intracellular enzymatic components and extracellular reduction. Sulphasalazine, used for the treatment of IBD saulphasalazine(5-ASA)is composed of sulphapyridine. This has antibacterial activity and 5-ASA which has anti-inflammatory activity and both drug link with azo bond. In the colon, the azoreductases cleave the azo bond releasing the drug, and the carrier sulphapyridine.[14]



3.1.2.2Dextran conjugated prodrug

Dextran is the carbohydrate and colonic flora use it as the energy source. Dextran hydrogel is used in colon site specific delivery of drug, various prodrug of dextran is synthesized with NSADS using ester link between the Dextran and -COO group of drugs molecule. After oral administration of as it reach in to the colon enzyme Dextanase present in human colon break the ester linkage of such conjugation and liberate free drug.

3.2 Polymeric approach to deliver intact drug molecule to colon

3.2.1 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 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.24 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.25 The decline in pH from the end of the small intestine to the colon can also result in problems, lengthy lag times at the ileo-cecal junction or rapid transit through the ascending colon which can also result in poor site-specificity of enteric-coated single-unit formulations.[17-18]

3.2.2 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.[19] The dosage forms may also be applicable as colon targeting dosage forms by prolonging the lag time of about 5 to 6 h.[20]

3.3 Time dependent delivery

3.3.1 Pulsincap

The first formulation introduced based on this principle was Pulsincap® developed by R.R. Scherer International Corporation, Michigan, US. It consists of non disintegrating half capsule body filled with drug content sealed at the opened end with the hydrogel plug, which is covered by water soluble cap. The whole unit is coated with an enteric polymer to avoid the problem of variable gastric emptying. When the capsule enters the small intestine the enteric coating dissolves and the hydrogel plug starts to swell. The length of the plug and its point of insertion into the capsule controlled the lag time. Diagram of pulsincap are shown in figure no.2. For water-insoluble drugs, a rapid release can be ensured by inclusion of effervescent agents or disintegrants. The plug material consists of insoluble but permeable and swellable polymers (e.g., polymethacrylates), erodible compressed polymers (e.g., hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g., saturated polyglycolated glycerides, glyceryl monooleate), and enzymatically controlled erodible polymer (e.g., pectin).[8]

3.4 Osmotic pressure controlled colonic DDS

Here the drug release form the device is achieved through an orifice by osmotic pressure generated inside the device. Metronidazole based on osmotic drug delivery system were formulate, this system consist of drug, osmogen (mannitol and fructose) this core were prepare by direct compression which were coat with semipermiable membrane which made by cellulose acetate, PEG400, guar gum, acetone, methanol, coating thickness of 90µm. This further coated with enteric polymer eudragit S100. During transit through GI this system remain intact in stomach due to coating of enteric polymer, but dissolve in small intestine pH and intestinal fluid enter into the tablet core react with osmogen and buildup osmotic pressure, as it reaches to colon the guar gum which is pore former is degrade by colonic micro flora forming pore and due to osmotic pressure core break result in drug release in colon.OROS_CT in which drug core is surrounded by semipermiable membrane and it is coating with enteric polymer. Delay drug release after 2-4 hr to prevent drug release in upper GI, this maintain constant drug release up to 24 hours and it is use in treatment of ulcerative colitis, crohn's disease.

COCLUSION

The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. CDDS offers considerable therapeutic benefits to patients in terms of both local and systemic treatment. Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes.

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