Review

RECENT APPROACHES FOR COLON CANCER: A REVIEW

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ABSTARCT

Cancer is one of the major public health problems worldwide. Prevalence of cancer is known to vary from region to region. The rapid socio economic changes have affected the prevalence and pattern of cancer. It is the third most common form of cancer and the second leading cause of cancer-related deaths in the western world. Colorectal cancer causes 655,000 deaths worldwide per year. Many colorectal cancers are thought to arise from adenomatous polyps in the colon. These mushroom-like growths are usually benign, but some may develop into cancer over time. Various factors like Transit through GI Tract, Stomach and intestinal pH, Colonic microflora affect the drug delivery to treat colon cancer. Various approaches are used to target the drug to the colonic area to treat colon cancer. Prodrug approach is the best approach to deliver the drug to the colon

KEYWORDS: Colon cancer, Pharmaceutical approach, drug delivery, Prodrug

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INTRODUCTION

Cancer

The origin of the word cancer is credited to the Greek physician Hippocrates (460-370 BC), who is considered the "Father of Medicine." Hippocrates used the terms carcinos and carcinoma to describe non-ulcer forming and ulcer-forming tumors. In Greek, these words refer to a crab, most likely applied to the disease because the finger-like spreading projections from a cancer called to mind the shape of a crab. The Roman physician, Celsus (28-50 BC), later translated the Greek term into cancer, the Latin word for crab. Galen (130-200 AD), another Roman physician, used the word oncos (Greek for swelling) to describe tumors. Although the crab analogy of Hippocrates and Celsus is still used to describe malignant tumors, Galen's term is now used as a part of the name for cancer specialists oncologists. Cancer is the second leading cause of deaths in the United States.[1,2]

Cancer is one of the major public health problems worldwide. Prevalence of cancer is known to vary from region to region. The rapid socio economic changes have affected the prevalence and pattern of cancer. The burden of cancer is growing, and cancer is one of the major determinants of the geographical patterns of cancer.[3] Cancer is a disease in which a group of cells display uncontrolled growth, invasion, and sometimes metastasis. These three malignant properties of cancers differentiate them from benign tumors, which are self-limited and unable to invade or metastasize. Cancer can occur in all living cells in the body and different cancer types have different causes of origin. The fact that the burden of cancer occurs mostly in the developed countries[4].

Gastro intestinal tract is divided into stomach, small intestine and large intestine. The large intestine extensing from the ileocaecal junction to the anus is divided into three main parts- colon, rectum and anal canal. In anatomy of digestive system colon primary purpose is to extract water from faeces. In mammals, it consists of the ascending colon to the right side, The transverse colon, descending colon to the left side, the sigmoid colon, and the rectum. Entire colon is about 5 feet long and 2.5 inches in diameter. It has a moist interior lining that protects nerves located in the colon wall. These nerves send and receive messages to the brain about the colon contents. The brain then directs the appropriate colonic action. Fluids and dietry fibre help to maintain colon health. Colon has a long transit time, near neutral pH, reduced digestive activity and an increased responsiveness to absorption enhancers. The absorbing surface area of the colon is $0.25m^2$. The usual colonic transit time varies from 20-30 hr. Bacteria live and grows along the colon lining. Using the fluids and foods you intake, bacteria actually manufacture the neutrient that sustain their environment and the food supply. The major function in the colon is the creation of suitable environment for the growth of colonic microorganisms, storage reservoir of faecal contents, expulsion of contents of the colon at an appropriate time and absorption of potassium and water from the lumen.[5]

Causes of Cancer:

Main factors are environmental factors and genetic factors[7] as shown in **Figure 1.**

Environmental factors: Environmental factors are mainly responsible for 80-90% of all human cancer. The major environmental factors identified as :

- Tobacco.
- Alcohol Dietary factor
- Viruses
- Parasites
- Customs habit and life styles.

Genetic factors: Genetic influences have long been suspected. For example, retinoblastoma occurs in children of the same parents. Mongols are more likely to develop cancer than normal children.

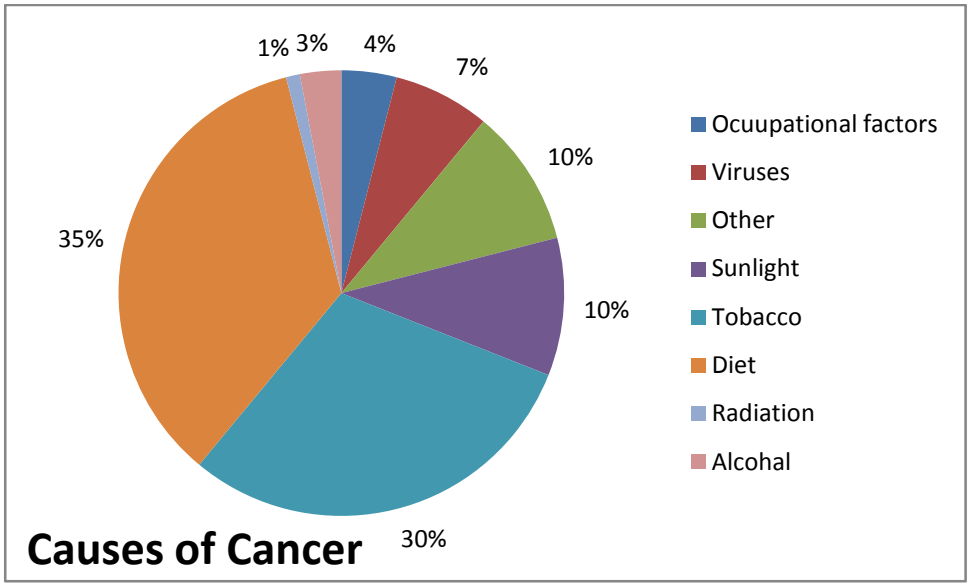


Figure 1: General Causes of Cancer

Global Impact of Cancer

- The colon and rectum (Colorectal cancer CRC) accounted for approximately 35000 cases and 55000 deaths in 1999.[6]
- In the Globocan 2002 database of the international agency for research on cancer (IARC), the worldwide burden of colorectal cancer is estimated as 550,000 incident new cases and 278,000 deaths for men, and 473,000 incident new cases and 255,000 deaths for women.
- Cancer-related deaths in the United States, with 145,290 new cases and 56,290 deaths anticipated in 2005.[7]
- It is estimated that more than 143,000 people will be diagnosed with CRC in 2012, and nearly 52,000 people will die from the disease.[8]

COLON CANCER

Anatomy and Physiology of Colon

Gastro intestinal tract is divided into stomach, small intestine and large intestine. The large intestine extensing from the ileocaecal junction to the anus is divided into three main parts- colon, rectum and anal canal. In anatomy of digestive system colon primary purpose is to extract water from faeces. In mammals, it consists of the ascending colon to the right side, The transverse colon, descending colon to the left side, the sigmoid colon, and the rectum. Entire colon is about 5 feet long and 2.5 inches in diameter. It has a moist interior lining that protects nerves located in the colon wall. These nerves send and receive messages to the brain about the colon contents. The brain then directs the appropriate colonic action. Fluids and dietry fibre help to maintain colon health. Colon has a long transit time, near neutral pH, reduced digestive activity and an increased responsiveness to absorption enhancers. The absorbing surface area of the colon is $0.25m^2$. The usual colonic transit time varies from 20-30 hr. Bacteria live and grows along the colon lining. Using the fluids and foods you intake, bacteria actually manufacture the neutrient that sustain their environment and the food supply. The major function in the colon is the creation of suitable

environment for the growth of colonic microorganisms, storage reservoir of faecal contents, expulsion of contents of the colon at an appropriate time and absorption of potassium and water from the lumen.[8]

Colonic Microflora : The sluggish movement of material through the colon allows a large microbial population to succeed there. Over 400 species of bacteria found, for the most part anaerobes and a small number of fungi.The bacterial count is 10^{11}-10^{12} CFU/mL in colon. Most of them are anaerobes *e.g. E.coli*. Among all of them 20-30% are bacteroides.[9,10]

Table 1 shows some of the colonic targeted disease , drug and sites.[11]

Target sites	Disease conditions	Drug and active agents
Topical Action	Inflammatory Bowel disease, Irritable bowel diseases and chrohn's disease, chronic pancreatitis.	Hydrocortisone, Budenoside, Prednisolone, Sulfasalazine
Local action	Pancreatactomy and cystic fibrosis, colorectal cancer	Digestive enzymes supplements, 5-fluorouracil
Systemic action	To prevent gastric irritation, to prevent first pass metabolism of orally ingested drugs.	NSAIDS, Steroids.

Table 1. Colon targeted disease, drug and sites

It is the third most common form of cancer and the second leading cause of cancer-related deaths in the western world. Colorectal cancer causes 655,000 deaths worldwide per year. Many colorectal cancers are thought to arise from adenomatous polyps in the colon. These mushroom-like growths are usually benign, but some may develop into cancer over time as shown in.[12]

Various stages of colon cancer

Colon cancer is assigned stages I through IV based on the following general criteria as shown in.[13]

- Stage I: The tumor is confined to the epithelium or has not penetrated through the first layer of muscle in the bowel wall.
- Stage II: The tumor has penetrated through to the outer wall of the colon or has gone through it, possibly invading other local tissue.
- Stage III: Any depth or size of tumour associated with regional lymph node involvement.
- Stage IV: Any of previous criteria associated with distant metastasis.

Various drugs are used for the treatment of colon cancer as shown in **Table 2**[14]

Glossary of Treatments for Colorectal Cancer	
FDA approved drugs	• Fluorouracil • Capecitabine (Xeloda) • Irinotecan (Camptosar) • Oxaliplatin (Eloxatin) • Cetuximab (Erbitux) • Bevacizumab (Avastin)
FDA-approved combination regimens	• IFL: Irinotecan, bolus fluorouracil, and leucovorin —first-line therapy • FOLFIRI: Irinotecan, infusional fluorouracil, and leucovorin— first-line therapy • FOLFOX: Oxaliplatin, infusional fluorouracil, and leucovorin— first- and second-line therapy • Intravenous fluorouracil and bevacizumab — first-line therapy • Cetuximab and irinotecan — therapy for EGFR-positive

Table 2: List of drugs for the treatment of colon cancer

2.3.1 Limitations and Challenges in Colon Targeted Drug Delivery

- One challenge in the development of colon specific drug delivery is to establish an appropriate dissolution testing method to evaluate the designed system *in vitro*.
- As a site for drug delivery, the colon offers a near neutral pH, reduced digestive enzymatic activity, a long transit time and increased responsiveness to absorption enhancers; the targeting of drug to the colon is very complicated. As the colon is situated in the distal part of the alimentary canal, the colon is particularly difficult to access. In addition to that, the wide range of pH values and different enzymes present throughout the GI tract, through which the dosage form has to travel before reaching the target site, which complicate the reliability and delivery efficiency.
- The drug to be in the solution form before it arrives in the colon for the successful delivery through the site or alternatively, it should dissolve in the luminal fluids of the colon, but this can be a limiting factor for poorly soluble drugs as the fluid content in the colon is much lower and it is more viscous than in the upper part of the GI tract.
- While designing a drug delivery system, the solubility of the drug is also a concern, because it may bind non specific way to dietary residue, intestinal secretions, mucous or faecal matter.
- Lower surface area and relative tightness of the tight junction in the colon can also restrict drug transport across the mucosa and into the systemic circulation.[15,16]

Factors Affecting Colonic Drug Delivery

Targeted site-specific delivery to the colon prevents loss of drugs which frequently occurs in the upper gastrointestinal tract due to degradation by brush-border enzymes or to small intestinal absorption. Such targeted dosage forms also allow the systemic delivery of drugs over a prolonged period, exploiting the reservoir function of the right colon, and enable the delivery of drugs locally for the treatment of diseases of the colon. The design of delayed-release systems for optimal drug delivery to the colon requires a detailed knowledge of the following factors:

Transit through GI Tract

Intestinal transit time is important for nearly all orally targeting delivery systems. Gastric emptying rate plays a key role in timely delivery of the dosage from to the colon after oral administration. The transit through the GI tract is highly variable and depends on many factors like the gastric motility both in the presence and absence of food.[17] However, the small intestinal transit time is very reproducible ranging from 3-4 h regardless of the factors like the particle size of the dosage form or the presence or absence of food.[18] As the colonic movements are very sluggish, the transit time of drug in the large intestine ranges from 20-30 h.[19] The mean colonic transit time in humans is reported to be 33 h in men and 47 h in women.[20]

Stomach and Intestinal pH

pH of different organs of GIT varies from stomach (pH 1-3) to large intestine (pH 7-8). Local pH within the lumen of the GIT can directly affect delivery systems, such as those relying on enteric coatings, and indirectly by altering local enzymatic activity. Several patients had colonic pH's ranging from 5.0 to 7.0. [21]

Colonic Microbial Flora

Colonic lumen hosts a large variety of microorganisms with the number of species varying from 40-400. The bacterial count in the colon is much higher around 10^{11}-10^{12} CFU/ml than that in the preceding sections of the GI tract, where the bacterial concentration is around 10^{3} CFU/ml. The contents of the colon also contain residual activity from the pancreatic peptidases.[22] The colonic cells are less developed and contain low levels of hydrolytic enzymes. Bai and Chang proved a Ceacal brush border membranes possess the lowest proteolytic activity.[23] Co-administration of other drugs and the nature of the disease tend to alter the activity of the colonic microflora.[24]

Gastrointestinal Disease State

Site of the disease is an indispensable issue to be dealt with while developing a successful targeted delivery system. IBD is comprised of two specific conditions: Ulcerative colitis (UC) and Crohn's disease (CD). In ulcerative colitis, sites of inflammation extend to the more proximal regions of the colon over time. In crohn's disease, the predominant site of inflammation is the distal ileum; between 30% and 40% of patients also have significant colonic involvement. Thus a delivery system specifically designed for the treatment of patients with ulcerative colitis, can also serve well in the treatment of a subset of crohn's disease patients with colonic involvement.[25]

Pharmaceutical Approaches To Deliver A Drug To The Colon

Specific targeting of drug to the colon is recognized to have several therapeutic advantages. By definition, an oral colonic delivery system should prevent drug release in the stomach and small intestine but allow complete release in the colon. It is a very challenging task as the formulation would be exposed to varying gastrointestinal conditions on passage through the gut to the colon. Overall, the physiological changes along the GI tract can be generally characterized,

with an increase in pH, enzymatic activity due to the presence of colonic microflora and fluid content. These gradual changes in physiological parameters are suitable as triggering elements to affect a sudden release of drugs in the colon.

A variety of approaches have been used to develop the systems for the purpose of achieving colonic targeting. The most commonly used targeting mechanisms are:

Prodrug approach: Site-selective prodrug activation by exploiting the relatively high response site activity of an enzyme, has been successfully achieved with targeted delivery to the colon. Using this approach, drug is coupled to a hydrophilizing promoeity that is susceptible to cleavage by enzymes secreted by the colonic microflora as illustrated in **Figure 1**. Within the colon, the bacterially derived enzymes catalyze the conversion of the prodrug to a more lipophillic drug that is now available for absorption through the colonic membrane.[26,27]

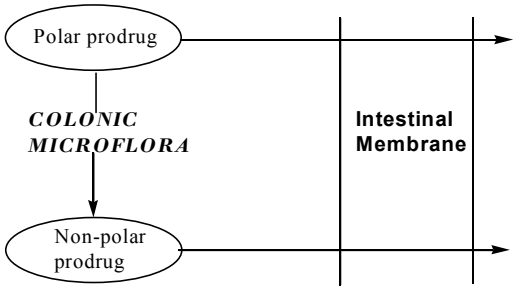


Figure 1: Mechanism of action of prodrug for targeted drug delivery to the colon

The biggest advantage of this system of drug delivery is its potential for patent protection. A newly synthesized compound can be easily patented as a composition of matter, which is generally considered the most desirable protection a potential product can obtain.[25]

Azo-bond conjugates

The intestinal microflora plays an indispensable role in a wide range of metabolic activities including the reduction of the nitro and azo groups in environmental and therapeutic compounds. The role of sulfasalazine as the first-line therapy in patients with inflammatory bowel disease has led to the development of other "designer" aminosalicylates, which eliminate the sulfa-moiety, and attempt to target the topically active mesalamine to the inflammed bowel.[28] Chemically, it is salicylazosulphapyridine (SASP) where sulphapyridine (SP), which has antibacterial action and 5-aminosalicylic acid (5-ASA), which has anti-inflammatory potency, joined by an azo-bond. On oral administration, a large percentage of the modified drug reaches the colon intact (by a combination of biliary excretion and non-absorption in the small intestine). In the colon sulfasalazine is converted to its constituent by *azo-reductases* associated with the bacterial microflora as shown in **Figure 2.** It has been demonstrated that 5-ASA is the active moiety while sulphapyridine is only a carrier, which might be responsible for side effects.[29]

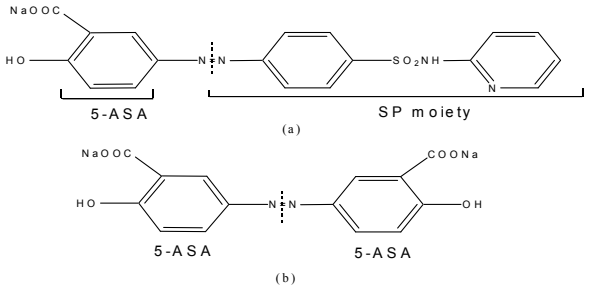


Figure 7: Sulfasalazine (a) and osalazine (b) prodrugs of 5-ASA The break line indicates the bond that is broken to produce the active agent

Olasalazine sodium and balsalazide disodium utilize the same azo-bond structure as sulfasalazine, requiring release of active mesalamine by colonic bacteria, and thus targeting these agents to the colon. Osalazine consists of two molecules of 5-ASA linked by an azo-bond.[30] By replacing the carrier molecule with other amino acids, a number of prodrugs of 5-ASA have been prepared e.g. aminohippurate (4-aminobenzoyl glycine) in ipsalazine, 4-aminobenzoyl-*β*-alanine in basalazine,[31] *p*-aminobenzoate in HB-313 (or a nonabsorbable sulphanilamide ethylene polymer in poly-ASA).[32] Leopold and friend (1995) investigated the ability of poly (L-aspartic acid) (weight-average MW: 30000) to act as a drug carrier for the model drug dexamethasone (DX).[33]

Glycoside and Glucuronide conjugates

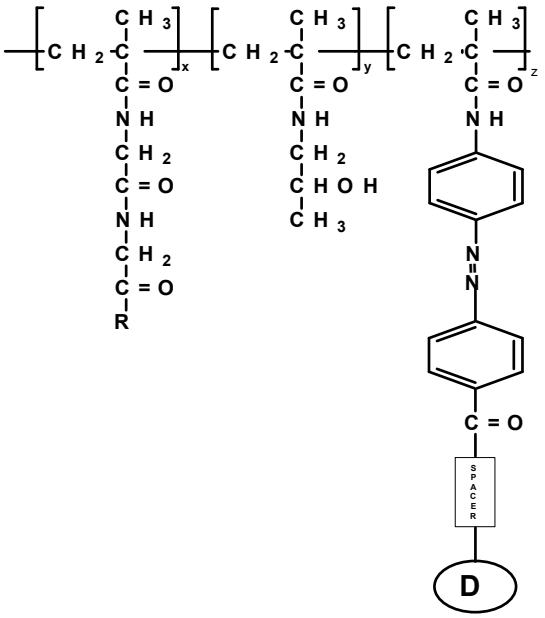
This approach involves exploitation of prominent bacterial enzymes such as *glycosidases* and *polysaccharidases* for targeting the drug to the colon. The enzymatic activities present in the colon cleave the drug glycosides, which results in the release of the free drug to be absorbed by mucosa of the colon. Once such a glycoside reaches the colon it gets cleaved by enzyme *glycosidases,* releasing free drug to be absorbed by the colonic mucosa. A number of studies have indicated that corticosteroids released from glycoside prodrugs are absorbed from the lumen of the large intestine and lead to much higher colonic tissue levels than are possible when the parent corticosteroid is administered systemically. Prodrugs of prednisolone, dexamethasone hydrocortisone and fludrocortisone with *β*-D-galactosides and *β*-D-glucosides have been prepared.[34,35]

Similarly, glucuronide prodrugs are also expected to be superior prodrugs for colon delivery. The treatment of ulcerative colitis was improved by the synthesis of budesonide and dexamethasone conjugates of glucuronic acid and dextran.[36,37] These systems show excellent performance in ulcerative colitis and also reduce the systemic toxicity of corticosteroids including adrenal suppression by increase of activity of drug in large intestine.

Polymeric prodrugs

Polymers containing azo groups are susceptible to degradation in a reductive medium. Polymeric prodrugs possess increased water solubility due to their large size and the presence of a biospecific targeting moiety in the structure. It also results in an alteration in the pharmacokinetics of the drug as compared to the unconjugated drug.[38] Dependent on the nature of the polymer the reduction can result in chain cleavage or can stop at the intermediate stage of hydrazine formation, which is useful as a coating for tablets designed for colon directed drug release.[39] A biodegradable spacer is also present in between the polymer carrier and the drug, it aids in controlling the site and rate of release of the active agent. Using this approach, N-(2-hydroxypropyl)methacrylamide (HPMA)

copolymer-9-AC conjugates containing an aromatic azo-bond and a 1,6-elimination spacer has been successfully designed by as shown in **Figure 3**.[40]



Spacer: 1,6 elimination spacer D: 9-Aminocamptothecan

Figure 3: Structure of colon-specific N-(2-hydroxypropyl) methacrylamide (HPMA) copolymer-9-AC conjugates

It results in a fast and highly efficient release of unmodified 9-AC from the conjugate by caecal contents *in vitro*. This conjugate has the potential of enhancing the therapeutic efficacy of 9-aminocamptothecan (9-AC) against colon cancer to reduce side effects due to local drug release. This approach can also be applied to other amino containing drugs (e.g. 5-ASA).

Recently, a lot of emphasis has been laid on dendrimers as drug-delivery systems. This agent not only incorporates a large number of drug molecules in the dendritic architecture but also aids in controlled release of the drug via hydrolytic cleavage of the ester bonds from the cascade architecture of the dendrimers.[41]

A prodrug using dendrimers as the carrier polymer for delivery of 5-ASA utilizing the azo-polymer approach.[42] The drug was bound to the dendrimer using two different spacers containing azo-bond, *p*-aminobenzoic acid (PABA) and *p*-aminohippuric acid (PAH). The major limitation offered by this system was a slower rate of release of the drug at the site of action. Another limitation offered by this system is that coupling of drugs with such high molecular weight polymers result in an increase in bulk of the final formulation. As a result of which it cannot be used for targeting of high dose drugs e.g. (5-ASA). Hence, the polymeric approach is of greater utility with potent drugs rather than drugs with a high dose (e.g. 5-ASA).

Cyclodextrin conjugates

Cyclodextrins (CD's) are cyclic oligosaccharides consisting of 6-8 glucose units. They are known to be barely capable of being hydrolyzed and only slightly absorbed in the passage through the stomach and small intestine and are fermented by colonic microflora into small saccharides. This peculiar hydrolyzing property of CD's makes them useful for colon drug targeting. The rate of

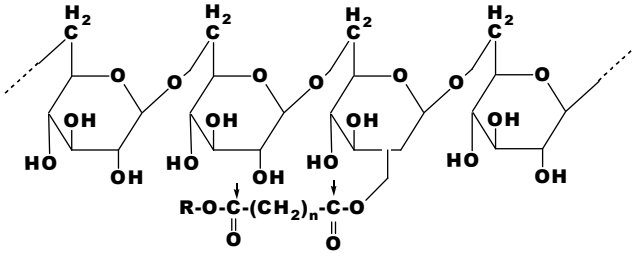
hydrolysis of the different types (*α, β* and *γ*) of CD's provides with a great deal of flexibility in design of the targeted delivery systems.[43] CD prodrugs for colon-specific delivery were developed by conjugation of the drug onto one of the primary hydroxyl groups of *α, β,* and *γ* CD's through an ester or amide linkage. In the case of ester prodrugs, the maltose and triose conjugates released the free drug after initial hydrolysis of the susceptible ester linkage, but in the case of amide prodrugs, the conjugates remained as such providing delayed release due to the resistance of the amide bond to hydrolysis.[44]

A number of cyclodextrin drug complexes have been synthesized for steroidal drugs. The general structure of prednisolone/α-CD conjugates and the subsequent release of prednisolone and prednisolone-21-hemisuccinate from the conjugates .

Zou *et al.,* (2005) conjugated anti-inflammatory drug 5-ASA onto the hydroxyl groups of *α, β* and *γ* cyclodextrins through an ester linkage, and investigated the *in vivo* drug release behaviour of these prodrugs in rat's gastrointestinal tract after the oral administration.[45] The 5-ASA concentration in the rat's stomach and small intestine after the oral administration of CD-5-ASA conjugate was found to be much lower than that after the oral administration of 5-ASA alone. The lower concentration was attributable to the passage of the conjugate through the stomach and small intestine without significant degradation or absorption, followed by the degradation of the conjugate site-specific in the caecum and colon. Therefore, CD-5-ASA conjugates were concluded to be potential candidates as prodrugs for colon-specific delivery system.

Dextran conjugates

Dextrans are basically composed of multiple, repeating glucose moieties. Compositionally dextrans contain a large number of hydroxyl groups. These drugs are used to link the drug to the polymer. Generally, it utilizes carboxyl groups in the drug and in the absence of these groups on the drug a spacer molecule is attached such as succinic acid and glutaric acid.[46] Harboe and coworkers (1989) conjugated naproxen to dextran by ester linkage. They observed that the release of naproxen increased to a considerable extent in the caecum and in the colon homogenates and in the homogenates of the small intestine.[47] **Figure 4** shows the structure of structure of dextran prodrug.[48]



n = 2 succinate n = 3 glutarate

Figure 4: Structure of dextran prodrug, where R represents the drug

Dexamethasone can be specifically delivered to the large intestine by using dexamethasone-dextran (M.W.260,000) conjugate.[49] The prodrug had a great potential in the treatment of inflammatory bowel disease. A colon-specific drug-delivery system was developed based on dexamethasone-succinate-dextran (DSD) conjugation and the unique glycosidase activity of

the colonic microflora was utilized for drug release.[50] A prodrug of nalidixic acid with dextran has been synthesized for colon specific delivery.[52] Dextran ester prodrug of metronidazole was also prepared and characterized by Johansen and Larsen, 1984; 1985, Vermeersch *et al.,* 1985.[52-54] *In vitro* results proved the efficacy of these prodrugs for delivering the drugs to the colon in sufficient therapeutic amounts.

Sulfated prodrugs

Many reports have suggested that the *sulfatase* activity in the gastrointestinal tract is of microbial origin and a higher activity is present in the large intestine as compared to the upper parts of the GIT.[55] Based on these studies it was concluded that sulfate ester prodrugs, synthesized by the introduction of a hydrophilic sulfate ester sodium group to the drug molecule, might serve as a promising colon-specific promoiety for glucocorticoids e.g. prednisolone 21-sulfate sodium. Kim and co-workers (2006) synthesized dexamethasone 21-sulfate sodium (DS) and assessed its potential as a colon-specific prodrug.[56] On incubation with the rat caecal content (5%) high amounts of drug was released in the caecum (~ 62%) and colon (~ 38%) after 24h. These results demonstrated that DS might be delivered specifically to the colon as an intact form to produce dexamethasone in high yield. Since the polymer used in the synthesis of polymer-linked prodrugs is polyphosphazene, therefore, it is in order to give a brief account of polyphosphazene.

Conclusion

As we all know colon cancer is the major health problem effecting a large population. Many drugs are used for the treatment of colon cancer, but they suffer from the side effect that they undergoes presystemic metabolism before reaching to the colon. Drug delivery to the colon cancer is a major health problem. Recently various approaches are used for the drug delivery to the colon out of them prodrug approach is the approach to target the drug to the colonic area.

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