ABSTRACT

Colorectal cancer develops from the polyps (outgrowths) formed into the distal part of digestive system. These polyps are known as adenomas and are precursors to cancer. Once the development of colorectal cancer starts, it can further spread to other body parts via lining and wall of colon and rectum. Depending on the stage of colorectal cancer, it can be treated either by chemotherapy, surgery, radiation therapy or by immunotherapy. Following chemotherapy various approaches have been employed by researchers for targeting drugs successfully to the colonic region by circumventing the upper part of gastrointestinal tract. These approaches include pH-dependent, time-dependent and microflora-activated systems. As colon is rich in aerobic and anaerobic microflora, thus microflora activated systems can be used efficiently to deliver drug molecule to the target site. Various drug molecules have been reported to treat and prevent colorectal cancer, provided an efficient carrier system is developed that can deliver drug molecule to the colonic region only. This review will mainly focus on some possible approaches which can be successful to achieve drug targeting to colon to treat colorectal cancer.

KEYWORDS: colorectal cancer, colon targeted delivery, colon cancer, drug candidates for colorectal cancer.

INTRODUCTION

Colon cancer is also known as colorectal cancer that involves the colon, the parts of large intestine and rectum. Colorectal cancer is known as the third most common cancer in the world and the second most common cause of deaths due to cancer. In 2008, colorectal cancer was the most common cancer in males according to the National Cancer Registry at King
Faisal Specialist Hospital and Research Centre, and the second most in females after breast cancer according to National Cancer Registry Ministry of Health, Saudi Arabis, 2003. Usually, the development of colorectal cancer takes place slowly over a period of 10 -- 15 years from noncancerous polyps that develop on the lining of colon or rectum. These noncancerous polyps are also known as adenomas. It has been reported that adenomas are common and about one-third to one-half of individual develops one or more adenomas. Although less than 10% of adenomas progresses to cancers, but it has been reported that about 96% of colorectal cancer are adenocarcinomas in nature. Once the commencement of growth of cancer takes place in the colonic region, it can further propagate through the lining and walls of the colon and rectum to distant parts of body. Conventional treatment of colorectal cancer is consists of chemotherapeutic agents, administration by parenteral route, which delivers the drug to both normal as well as cancerous tissues, thus leading to numerous undesirable effects. Enormous research is going on worldwide for designing an alternative route of administration, among which oral colon-targeted drug delivery systems have gained immense attention amongst scientific community. Direct delivery of drugs at the site of action leads to an increase in the availability of drugs at the targeted region and also smaller amount of drug is required to exert same therapeutic effect as that of conventional route. This, in turns reduces the dose related side effects. Various approaches have been used by researchers for targeting drugs successfully to the colonic region by circumventing the upper part of gastrointestinal tract. These approaches include pH-dependent, time-dependent and microflora-activated systems. The most commonly used drug candidates for the treatment of colorectal cancer comprises of 5-fluorouracil (5-FU), leucovorin, oxaliplatin and capecitabine. Apart from these, other drug molecules that have been reported to play a significant role in prevention of colorectal cancer are meloxicam, curcumin, valdecoxib, resveratrol, indomethacin, celecoxib, methotrexate, gemcitabine, transcutol and ginger extract.\textsuperscript{[1,2]}

**APPROACHES USED TO ACHIEVE COLON TARGETED DELIVERY**

1) **Primary Approaches**

To achieve colon targeted delivery several approaches has been used. Among these following are the primary approaches
1.1. Coating with pH Sensitive Polymer
The pH range for the gastrointestinal tract starting from the oral cavity to rectum varies from 1 to 7.5. In the stomach, pH ranges from 1 to 3. Reaching proximal part of small intestine pH becomes about 6.5 and about 7.5 in the distal small intestine. It is about 6.4 in the cecum. In the transverse colon pH is 6.6 and 7.0 in the descending colon. Use of pH dependent polymers is based on these differences in pH levels. The pH sensitive polymers used are mostly insoluble at low pH levels but become increasingly soluble as pH rises. Although a pH dependent polymer can protect a formulation in the stomach, it may start to dissolve in the lower small intestine posing difficulty to achieve colon targeting release.

Zhang et al., (2012) prepared Curcumin-loaded folate modified self micro emulsifying drug delivery system. The system has been reported to improve solubility and achieve colonic targeting of curcumin as an anticancer agent. This system was further filled into a capsular system and capsules were further coated with Eudragit_ S 100. In vitro drug release studies showed that the formulation could deliver the drug efficiently to the colonic region. Also, cell uptake studies depicted that the system could bind efficiently with the folate receptors.

Nanogels of 5-FU as pH-dependent system has been reported by Ashwanikumar et al., (2012). These nanogels were prepared by microemulsion polymerization technique using methacrylic acid and 2-ethyl hexyl acrylate copolymers. 5-FU entrapment within the polymeric backbone was achieved using solvent evaporation method. In vitro drug-release studies revealed pH dependent release of drug in a sustained manner. The cell proliferation assay performed using HCT-116 cell lines revealed that the prepared formulation demonstrated significant cytotoxic effect compared with free 5-FU.

1.2. Time Controlled Release System
Due to large variation of gastric emptying time, appropriate integration of pH sensitive and time release functions into a single dosage form may improve the site specific delivery of drug molecule to the colon. As the transit time in the small intestine is less variable i.e. about 3±1 hr. (30), the time release system may offer advantage to release drug molecule in small intestine as compared to stomach. The system consists of three components: (i) core (containing drug molecule) (ii) swellable hydrophobic polymer layer, (iii) an enteric coating layer which makes it acid resistant. Due to acid resistance of the outer coating drug is not released in stomach. By reaching to small intestine after gastric emptying enteric coating layer rapidly dissolves and hydrophobic polymer starts swelling. Swelling of hydrophobic
polymer layer leads to erosion of core tablet which takes usually a long time, hence drug release is achieved in the colon.

1.3. pH and time-dependent systems

Different dosage forms have been reported having pH and time-didependent release profile. Following are the systems reported:

A dually coated drug-loaded microparticulate system using celecoxib has been reported. The system was prepared using a time- and pH-dependent approach. For time-dependent release coating with Poly-caprolactone was done and for pH-dependent release coating with Eudragit_S100 was done. In vitro drug release studies revealed that the double coat provides a satisfactory protection required for achieving colonic targeting. Also, in vivo pharmacokinetic study in rats revealed that the microparticles enhanced the bioavailability of drug and extended the duration of drug-plasma concentration.[9]

Formulation of dually coated tablets of meloxicam has been reported. These tablets were prepared by direct compression method. Tablets contained polyethylene oxide as release retardant. The outer coat of tablet consists of pH-dependent polymer e.g. Eudragit_FS 30D and inner coat consists of time dependent layer of ethyl cellulose containing polyethylene glycol. In vitro dissolution studies shown that the developed system remains intact and prevents premature drug release in upper part of GIT. In vivo pharmacokinetic and roentgenography studies in rabbits shown that the prepared formulation remained intact until it reaches to the lower part of GIT.[10]

Pellets containing 5-FU dually coated with Eudragit_NE30D (time dependent layer) and Eudragit_FS30D (pH dependent layer) has been developed. Pellets were prepared by extrusionspheronization technique using Avicel PH101 as a spheronization aid and HPMC K4M as a binder. In vitro drug release studies shown that pellets coated with 15% w/w of inner and outer coating level was found to be optimum for achieving colon targeting.[11]

1.4. Microbial Triggered delivery system

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 beneficial as compared to other approaches.[12] The microflora of the colon mainly consists of anaerobic bacteria, e.g. bacteroides, enterobacteria, bifidobacteria, enterococci, eubacteria, clostridia, and ruminococcus etc.[13] These bacteria produce enzymes like glucoronidase, xylosidase,
arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase whose major function is reduction and hydrolysis.\cite{14} These enzymes help microflora to fulfil their energy requirements by fermenting various types of substrates that have been left undigested in the small intestine, e.g. di- and tri-saccharides, polysaccharides etc[15,16]. Biodegradable polymers protect the drug molecule in the stomach and small intestine, and are able to deliver the drug to the colon. On reaching the colon, they undergo degradation by enzyme or break down of the polymer back bone leading to a subsequent reduction in their molecular weight.\cite{17,18,19,20,21} Once they lost their mechanical strength, they become unable to hold the drug entity any longer and release of the drug molecule takes place into colon.\cite{22}

1.5. Prodrug Approach for Drug Delivery to Colon

Prodrug is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation \textit{in vivo} to release the active drug. For colonic delivery, the prodrug is designed to undergo minimal hydrolysis in the upper tracts of GIT, and undergo enzymatic hydrolysis in the colon there by releasing the active drug moiety from the drug carrier. Metabolism of azo compounds by intestinal bacteria is one of the most extensively studied bacterial metabolic processes.\cite{23} A number of other linkages susceptible to bacterial hydrolysis especially in the colon have been prepared where the drug is attached to hydrophobic moieties like amino acids, glucoronic acids, glucose, lactose, cellulose etc. As the formulation of prodrug depends upon the functional group available on the drug moiety for chemical linkage so this approach is not versatile. Furthermore, prodrugs are new chemical entities, and need a lot of evaluation before being used as carriers.\cite{24}

1.5.1. Azo-Polymeric Prodrugs

Newer approaches are aimed at the use of polymers as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers have been used for this purpose. Sub synthetic polymers have been used to form polymeric prodrug with azo linkage between the polymer and drug moiety.\cite{25} These have been evaluated for colon targeted delivery. Various azo polymers have also been evaluated as coating materials over drug cores. These have been found to be similarly susceptible to cleavage by the azoreducatase in the large intestine. Coating of peptide capsules with polymers cross linked with azoaromatic group has been found to protect the drug from digestion in the stomach and small intestine. In the colon, the azo bonds are reduced, and the drug is released.\cite{26}
An azo-based polyphosphazene drug conjugates of methotrexate and gemcitabine has been prepared and evaluated for colon targeted delivery. The conjugates were found to be stable in presence of acidic conditions and were reported to release more than 89% of drug in presence of rat cecal contents. In vitro cytotoxicity study revealed that the prepared azo-conjugates are active against HT-29 and COLO 320 DM (human colorectal cancer cell lines), depicting the potential of the prepared system to release the drug into the colon.\cite{27}

The use of naturally occurring polysaccharides is attracting a lot of attention for drug targeting the colon since these polymers of monosaccharides are found in abundance, have wide availability are inexpensive and are available in a wide range of structures with a variety of properties. They can be easily modified chemically, biochemically, and are highly stable, safe, nontoxic, hydrophilic and gel forming and in addition, are biodegradable. Therefore, they fall into the category of “generally regarded as safe” (GRAS).

These include naturally occurring polysaccharides obtained from plant (guar gum, inulin), animal (chitosan, chondroitin sulphate), algal (alginites) or microbial (dextran) origin. The polysaccharides can be broken down by the colonic microflora to simple saccharides.\cite{5}

1.6. **Microbially and/ or enzymatically driven drug delivery systems**

a) An Assam Bora rise starch has been evaluated for its efficiency for colon targeted delivery of 5-FU. Mucoadhesive microspheres were prepared by double emulsification solvent evaporation technique. In vitro dissolution studies revealed a small amount of drug release in upper part of GIT and a significant release in presence of rat caecal content. In vivo evaluation of the prepared formulation revealed that majority of drug got distributed to the lower part of the GIT depicting the potential of the developed system for colon targeting.\cite{28}

b) Paclitaxel-loaded chitin nanoparticulate system has been reported. These nanoparticles were prepared by ionic cross-linking reaction technique. In vitro drug release studies revealed sustained release behaviour of the prepared nanoparticulate system. Cell uptake study of the developed system was confirmed by fluorescent microscopy and flow cytometry. Anticancer activity of the developed system was determined by toxicity studies toward colon cancer cell lines.\cite{29}

c) Pellets containing 5-FU consisting of pectin as both coat and core material has been formulated and evaluated for colon targeting. Ethyl cellulose was employed as an in situ
intracapsular coating material. *In vitro* evaluation revealed that less than 25% drug was released in upper part of GIT that demonstrated the potential of the developed system for achieving colon targeting.\[30\]

d) Methotrexate loaded folic acid and guar gum nanoparticles have been reported that were prepared by emulsification cross-linking technique. It has been reported that the percent growth inhibition of Caco-2 cells with methotrexate-folic acid-guar gum nanoparticles was higher than that of methotrexate-guar gum nanoparticles indicating folate receptor mediated uptake of the developed system.\[31\]

e) A calcium pectinate matrix tablet for colonic delivery of meloxicam microsponges were prepared by modified quasi-emulsion solvent diffusion technique. *In vivo* fluoroscopy in rabbits revealed that the calcium pectinate matrix released the drug-loaded microsponges selectively into the colonic region. *In vivo* pharmacokinetic study revealed a lag time of 7 h for appearance of drug in plasma proving the potential of developed system for colon targeting.\[32\]

f) Compression-coated tablets containing 5-FU as drug candidate was evaluated as a potential alternative for achieving colon targeted delivery. Granulated chitosan was employed as a compression coat. *In vitro* drug release studies revealed that the granulation of chitosan provides protective action against the acidic environment of the upper part of GIT. Roentgenography study in beagle dogs was carried out which revealed that the developed system was resistant to the conditions prevailing in upper part of the GIT and selectively release the drug in the lower part of GIT.\[33\]

g) A novel microbially triggered colon targeted delivery system of 5-FU was developed using pectin and starch paste as biodegradable material. *In vitro* evaluation of the optimized formulation revealed negligible amount of drug release at pH 1.2 and 7.4, whereas significant amount of drug release was observed at pH 6.5 in presence of rat caecal content. *In vivo* pharmacokinetic and roentgenographic evaluation in rabbits revealed the potential of the developed formulation for colon targeting.\[34\]

1.7. pH and microflora activated di-dependent systems

a) Eudragit_ S 100 coated valdecoxib-loaded sodium alginate microspheres of valdecoxib have been reported that were evaluated for achieving colon targeted delivery. The *in vitro* cell
line studies revealed that the transport of valdecoxib microspheres across Caco-2 cell monolayers at pH 7.4 was found to be slower than that of solutions, thus providing a prolonged and sustained release profile.[35]

b) Eudragit® S 100 coated calcium pectinate microspheres containing curcumin were prepared by emulsification cross linking technique. *In vitro* evaluation of the developed system revealed that the drug release was significantly increased in presence of rat caecal content (1% w/v).[36]

c) Eudragit® S 100 coated ginger extract-loaded alginate beads were prepared for treatment of colorectal cancer. *In vitro* evaluation of the developed systems revealed a super class II release mechanism, controlled by swelling and polymer relaxation. Preclinical evaluation in male Wistar rats revealed that the developed system could significantly reduce the growth of cancer after four weeks of treatment.[37]

2. Newly Developed Approaches for colon targeted delivery

2.1. Pressure Controlled Drug-Delivery Systems

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. Pressure controlled colon-delivery capsules have been prepared using ethyl cellulose, which is insoluble in water.[38] 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.[39,40] 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 form.[41] Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to humans.

2.2. Novel Colon Targeted Delivery System

CODESTM is a unique colon targeted delivery technology that was designed to avoid the inherent problems associated with pH or time dependent systems.[42,43] CODESTM is a combined approach of pH dependent and microbially triggered colon targeted delivery. 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 overcoated 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. Once the tablet arrives in the colon, the bacteria enzymatically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH surrounding the system sufficient to affect the dissolution of the acid soluble coating and subsequent drug release.

2.3. Osmotic Controlled Drug Delivery (ORDS-CT)

The OROS-CT (Alza Corporation) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise difficult to attain. The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule. Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. An orifice is drilled through the membrane next to the drug layer. Immediately 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 (pH >7), water enters the unit, causing the osmotic push compartment to swell, and concomitantly creates a flow able 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 h 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 hours in the colon or can deliver drug over a period as short as four hours. Recently, new phase transited systems have come which promise to be a good tool for targeting drugs to the colon. Various in vitro / in vivo evaluation techniques have been developed and proposed to test the performance and stability of colon targeted delivery system.
CONCLUSION
This is the high time to develop a drug carrier system that can remain intact in the upper GIT and can deliver drug molecule in the proximity of cancer cells in colon and rectum. Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. In future by combining various strategies, colon targeted drug delivery will find the central place in novel drug delivery system.

Ongoing Research on treatment of colorectal cancer
In search of more effective treatments many combinations of drugs that are already used separately to treat colorectal cancer are under clinical trials. A new colon cancer vaccine, monoclonal antibody therapy, radio-immunotherapy, imaging-guided and robot-assisted surgery and molecular-targeted therapies are among other new approaches to treating advanced colon cancer. More clinical trials are studying the addition of targeted therapy such as bevacizumab or cetuximab to chemotherapy as first, second and third choice therapies for the treatment of colorectal cancer.

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