Advances in orally targeted drug delivery to colon

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ABSTRACT

Colon-specific drug delivery is critical for treating diseases of colon, such as colon cancer, amoebiasis, irritable bowel syndrome, and inflammatory bowel disease. This study reviews the effects of targeted oral drug delivery on patient by measuring the accurate administration of the drug to specific disease spot, thus enhancing the therapeutic efficacy and provides better therapeutic outcomes. Medically targeted delivery to colon produces local effect on the diseases and hinders the systemic toxic effects of drugs. The delivery of therapeutics to the specific diseased part of colon has its merits over systemic drug delivery, albeit has some obstacles and problems. Colon drug delivery can be used to create both systemic and local effects. Many advanced approaches are used, such as conventional methods for drug release to colon, delayed release dosage forms, nanoparticles, carbon nanotubes, dendrimers, and alginate coated microparticles. This concise review summarizes and elaborates the details of different techniques and strategies on targeted oral drug delivery to colon as well as studies the advantages, disadvantages, and limitations to improve the application of drug in the part of the affected colon.

Key words: Alginate, carbon nanotubes, dendrimers, drug delivery, microparticles, nanoparticles

INTRODUCTION

Oral route for drug administration is considered the most convenient way due to its simplicity, effectiveness, and being noninvasive method.¹ Thus, orally targeted drug delivery to colon is center of interest to treat different localized diseases, inflammatory bowel syndrome, ulcerative colitis (UC), Crohn’s disease, and colorectal cancer (CRC).² On account of high prevalence of CRC, 1.3 million people are diagnosed with CRC per year, rated as the third deadliest cancer in world.³ Furthermore, inflammatory bowel disease (IBD), UC, Crohn’s disease, and CRC need a longer duration for treatment.⁴ Colon Specific Drug Delivery targets direct treatment at the diseased spots, prevents metabolism of drug in liver due to first pass metabolism, and decreases absorption of drug to system, thus enhances therapeutic efficacy.⁵ Merits and demerits of CTDDs in different dosage forms has been further discussed in Table 1. Nevertheless, there are some obstacles and problems to get to this target, as gastrointestinal (GI) tract has different regions in varying environments with different pH, for example, hostile pH of the gastric region, first-pass metabolism, GI Transit, enzymes in small intestine, normal flora, and bacterial enzymes of large intestine itself. These conditions can be highly variable in the condition of diseased conditions from patient to patient. It could have significant effects on the purpose of colonic-specific drug delivery, as shown in Figure 1. Therefore, drugs need to be protected from such conditions. In this way, newer drug delivery approaches are applied, such as nanoparticles (NPs), Micro Matrix Systems,
polymer-based formulations, polysaccharide-based micro/nano beads, and so forth.\[^5\]

For decades, different approaches have been used to obtain specific Targeted Oral Drug Delivery conventional strategies are presented in Figure 2. In prodrug approach, inactive pharmacological drug will undergo enzymatic transformation such as of 5-aminosalicylic acid (5-ASA), sulfasalazine, or olsalazine, as shown in Figure 3, is cleaved by the enzymes of colonic bacteria into active metabolites.\[^6\] Azo-based anticancer prodrugs such as methotrexate, oxaliplatin, and gemcitabine have been figured out.\[^7\] Another double prodrug novel approach was studied for benzenesulfonamide cyclooxygenase-2 inhibitor using celecoxib, i.e., activated by azoreductase enzyme before releasing the drug by cyclization.\[^8\] In cancer therapy, high doses of anti-tumor drug molecules are usually delivered to achieve maximum efficacy. However, this high dose can induce toxicity to normal organs; thus, it is recommended to produce dosage forms such as prodrugs, drugs loaded inside microspheres, liposomes, NPs, and carbon nanotubes (CNTs).\[^9\] Xylan-5-fluorouracil conjugated to acetic acid are fabricated as a prodrug for colon cancer treatment. It shows a potential increase in drug release with reduced cytotoxicity.\[^10\] Polymers have a great contribution in drug delivery to colon on the basis of their nature that solubilize in specific pH, can stabilize active pharmaceutical ingredient, and can control drug release, and can also be incorporated in novel systems that can eventually improve their applications and properties by working as vehicles and drug carriers.\[^11\] Chitosan is a naturally based polymer that has been applied in the formulation of chitosan-coated poly(lactic-co-glycolic acid) (PLGA) NPs, they are excellent carriers for delivering proteins in their active form to specific organs.\[^12\] The formulation of chitosan-succinyl-prednisolone encoated in Eudragit L microspheres were reported by Vats et al. that toxic side-effects of drugs were reduced in rats with colitis.\[^13\] The following peer review presents strategies and new approaches used to target colon by administering the drug orally.

**MINITABLETS APPROACH**

Hadi et al, reported colon targeted minitablets of lornoxicam and naproxen in hidroxy propyl methyl cellulose capsule shell for rheumatoid arthritis treatment provided a uniform drug release and an excellent patient compliance.\[^14\] These mini-tablets processing includes different techniques of formulation like the use of polymers that release drug in time-dependent manner called core mini-tablets filled with pulsincap, employing pH dependent and microsomal enzyme-dependent polymers, that are known as capsules filled with matrix mini-tablets or filled with coated mini-tablets by utilizing pH-dependent polymers.\[^12\]

**MICROSHERES**

Biodegradable polymers or protein-based microspheres having free-flowing properties and particle size 5200 nm have a variety of advantages over conventional drug delivery systems. Where the environmental factors are highly variable from patient to patient and in different diseases, they can provide localized delivery, sustained
delivery, and stabilization of the sensitive drug. Different kinds of matrices used in these microspheres are observed, one of them is polysaccharide-based microspheres that were introduced by Zhang et al. A combination of prodrug approach along with multiparticulate system is reported by Vaidya et al., who explained the production of pectin metronidazole microspheres for amoebiasis treatment. A microemulsion loaded with 5-ASA silicon dioxide NPs were formulated by Tang et al. for UC, with lower cytotoxicity and better efficacy.

**MUCOADHESIVE APPROACH**

Valdecoxib mucoadhesive matrix prepared with sodium alginate and coated inside Eudragit S 100 as an anti-inflammatory drug was reported by Zhang et al. in micro and nanocarriers for colonic drug delivery. Naproxen sodium mucoadhesive polymer made of sodium alginate and eudragit S100 for the treatment of colitis was prepared by Chawla et al. NPs with better mucoadhesive properties are developed as reported by Chuah et al. The production of NPs made of curcumin and chitosan have a mucoadhesive drug delivery potential, thereby increasing bioavailability.

**MULTIMATRIX SYSTEMS**

Multi-matrix systems have been produced to provide single-dose therapy, enhancing patient compliance, and efficacy of therapy. Fiorino et al. reported the multi-matrix system of mesalamine as a single dose for therapy of UC.
and treatment of IBD. Time-dependent delivery system was used in the fabrication of dosage form for delivery of insulin to colon, as indicated by Maroni et al. chronotopic system where insulin was loaded into cores and coated with hydroxypropyl methylcellulose by spray drying method, with the assessment of long-term stability and efficacy.

**NANOPARTICLES**

NPs include different types such as metallic NPs, CNTs, biodegradable polymers, and dendrimers, used in targeting drug delivery to colon are discussed briefly. NPs with their distinct and distinguished properties have shifted the medicine industry. For instance, doxorubicin loaded inside polyacrylic acid a pH-sensitive polymer with mesoporous silica SBA-15 by grafting strategy, to improve efficacy and safety of drug with good bioavailability high drug loading of 785.7 mg/g and awesome pH-susceptibility was reported by Tian et al. Enzyme responding mesoporous silica NPs of 5-fluorouracil capped inside layer of guar gum was fabricated that had an excellent drug release in the presence of enzymes. Ayub et al. reported improvement in the delivery of paclitaxel to cancerous cells of colon, by producing nanospheres with a layer by layer approach of cysteamine-based disulfide cross-linked sodium alginate, that had more than 70% of cell internalization. Theiss et al. reported NPs delivered in hydrogel fabricated by the electrostatic interactions among sulfate ions or calcium ions of alginate and chitosan to crosslink, and these crosslinks are cleaved by colonic enzymes that make drug bioavailable. Alginate/chitosan hydrogel containing anti-inflammatory peptide Lysine-Prolin-Valine encapsulated inside NPs, that more than 70% of cell internalization.

**LIPOSOMES**

Liposomes are phospholipid bilayer vesicles of nanosize that have been in use for targeted colon drug delivery as explicated by Garg et al. PEGylated Doxirubicin liposomes were reported by Alberto Gabizon that showed decrease in macrophage recognition, better biocompatibility, enhanced half-life. 5-fluorouracil loaded liposomes with folic acid as ligand to target colon cells was prepared, and it is in vivo efficacy was studied where 5-FU liposomes revealed better activity in killing cancer cells. Doxorubicin-loaded liposomes were fabricated and tested on Caco 2 colon cancerous cells by Neuberger et al., showed better circulation time, better drug internalization, and much lower cytotoxicity.

**MAGNETIC NANOPARTICLES**

Heating power is generated from the magnetic fluctuation (alternating magnetic field [AMF]) in magnetic NPs (MNPs) that has been extensively applied in biomedical, particularly as a novel method for cancers and tumors therapies. A previous study from Mannucci et al. shows that the natural fabrication of MNPs produced by magnetotactic bacteria is generated from MSR-1 strain of Magnetospirillum gryphiswaldense. It is anti-neoplastic activity on human colon carcinoma HT-29 cell cultures and its interaction to cells on in vivo level was assessed, that showed better uptake with no evidence of being cytotoxic.

On the other hand, thermotherapy is a potent tool used in therapy of many types of tumor, unfortunately, it has poor specificity. A variety of approaches are proposed and utilized to elevate the efficacy of the technique. In this way, magnetic fluid hyperthermia goes through AMFs in which it increases tissue temperature, hence maximizing the efficiency of the method by enhancing the intra-tumoral delivery of MNPs. Creixell et al. state that the production of epidermal growth factor (EGF) adjusted to carboxymethyl dextran and encapsulated iron oxide MNPs with a better internalization in cells is monodisperse and stable, as compared to nontargeted NPs.
DENDRIMERS

Dendrimers are the drug delivery systems that have excellent conjugation capacity as well as good encapsulation capacity. Recently, different types of dendrimers have been formulated and used in cancer research for targeted drug delivery. Dendrimer(s) are molecules that are linked to biologic molecules at cellular level covalently, to DNAs, folic acid, antibodies, chemotherapeutics, and contrast agents used for magnetic resonance imaging. Dendrimers conjugated to specific antibodies are more sensitive and can be extensively used to detect circulating tumor cells in detecting cancer.[56] 5-ASA was delivered to colon by dendrimer conjugates designed with polyamidoamine that is soluble in water, that was reported to have good resistance to drug release before reaching colon.[57]

CARBON NANOTUBES

Liu et al. report that the production of single-walled CNTs (SWNTs) of paclitaxel that have high suppressive activity on tumors in which the paclitaxel is insoluble in water, is linked to poly ethylated SWNTs. Consequently, it increases the water solubility and decreases the toxicity in normal cells.[58] As studied by Lee et al. reported the production of C225 antibody inside SWNTs intended for targeted therapy of EGF receptor that are mostly over-expressed in colon cancer. SN38 (7-ethyl-10-hydroxycamptothecin) activity on tumors in which the paclitaxel is insoluble in water, is linked to poly ethylated SWNTs. Consequently, it increases the water solubility and decreases the toxicity in normal cells.[59] Based on the discussion of this study supported by different international journals, it is revealed that targeted drug delivery to colon is necessary. Moreover, it can maximize the therapy target, reduce drug-related adverse reactions, and drug cytotoxicity. Newer approaches such as NPs, use of polymers have enhanced therapeutic outcomes.

CONCLUSION

The strategic approaches for localized colon diseases therapies still remain an emerging field of interest with so many obstacles to focus on over time. To sum up, this study demonstrates several conventional approaches that are enhanced by the application of new technologies, making them effective in colon cancer treatment. In this regard, Nanomedicine as an emerging field has revolutionized the medicine industry and enlightens effective treatment observation of cancer around the world. That assures a controlled drug delivery to the affected spot, increasing the efficacy and decreasing the drug-related side effects. As a result, it potentially improves patient compliance and also enhances quality life of affected patients. Although many of the nano-formulations are still under research and clinical trials, a variety of crucial nanotechnological applications have been used in humans and employed in cancer evaluations, early detection, and therapy. Until now, more research and novelties are insured to legitimize the productiveness and specificity of therapies that synergizes the localized effects to treat colon diseases and to thrive thousands of opportunities lying ahead in the future. As colon is a site that functions to excrete metabolic wastes and fewer amounts of products are being absorbed in this region, thus more research is needed in this era.

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Conflicts of interest

There no conflicts of interest.

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