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Review

Colon cancer targeting using conjugates biomaterial 5-fluorouracil



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ABSTRACT

There has been several research works on the development of an oral delivery system to deliver cytotoxic and chemo preventive agents directly at the targeted site of action with reduced unwanted side effects. The efficacy of the site-specific delivery system of a drug to colon has been proven to increase the drugs concentration at the target site, and thus requires a reduced dose of the drug with minimized side effects. This review includes discussion of the delivery systems of 5-FU using biodegradable materials and some significant outcomes in the pre-clinical development of 5-fluorouracil carriers for the colon cancer.

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Contents

1. Introduction	780
2. Colon cancer: causes and etiology	781
2.1. Delivery routes	782
2.2. 5-Fluorouracil	782
2.3. Fluorouracil delivery systems	783
2.4. Biodegradable materials	783
2.5. Alginate beads	783
2.6. Poly(E-caprolactone) (PCL)	784
2.7. EUDRAGIT [®]	784
2.8. Guar gum	784
3. Bovine serum albumin (BSA) nanoparticle	785
3.1. Poly(D,L-lactide) (PLA) and poly(D,L-lactide-co-glycolide) (PLGA)	785
4. Preclinical research studies with 5-fluorouracil delivery systems	785
5. Delivery system	785
6. Conclusion	786
Declaration of interest	786
Acknowledgments	786
References	786

1. Introduction

Colorectal cancer (CRC) is the third deadliest and widely diagnosed cancer in the world, accounting for 10% of all cancers [1]. Around 55% of colon cancer cases were diagnosed in Australia and New Zealand with its high prevalence among elders with a median age of 69 years old [2]. Approximately in a year, 5,60,000 people are lost to colon cancer worldwide. Colon cancer has a high metastatic and it's insensitive to metastatic in the liver and as such, there is a

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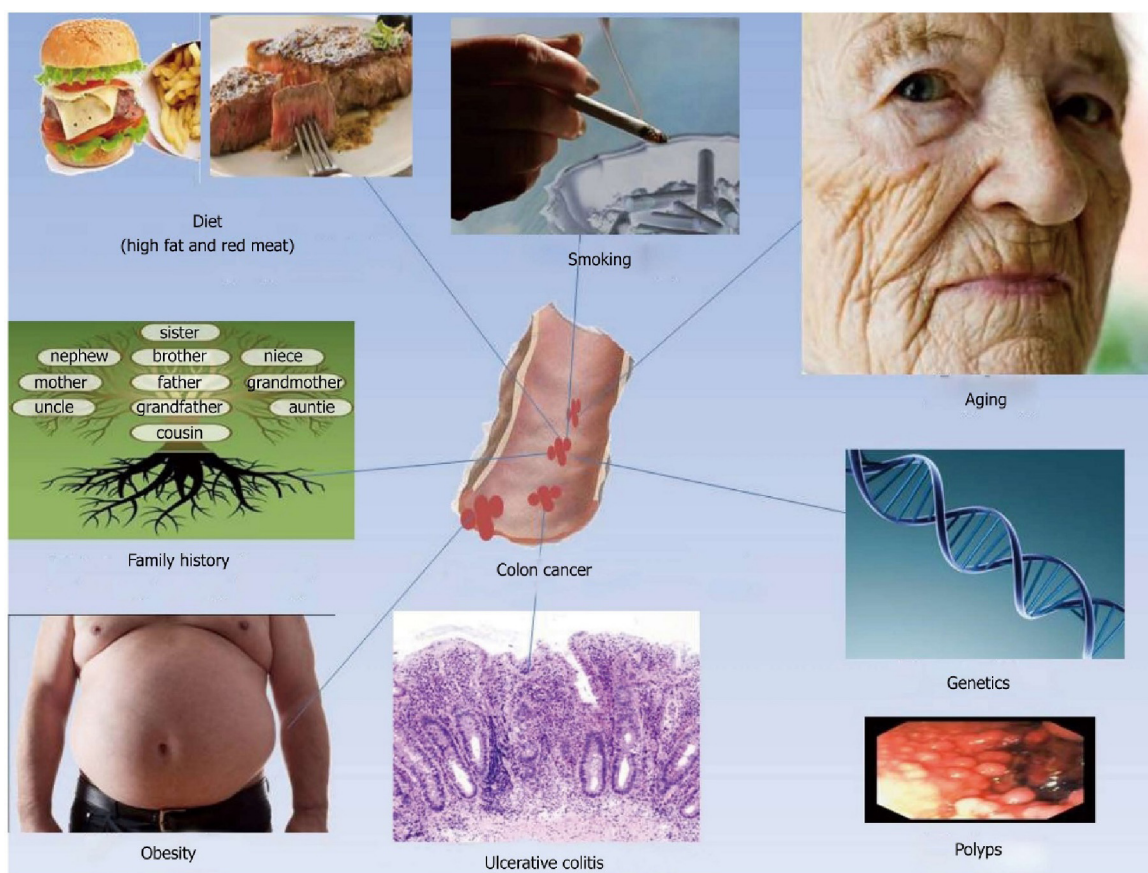


Fig. 1. Showing some causes of colorectal cancer. Several factors have been identified as causative agents of CRC that such as the diet with high fat and red meat, smoking, aging, family history, obesity, ulcerative colitis and polyps. This figure was. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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need to develop a new resistance mechanism [3–7]. Cytotoxic drugs are made of heterogeneous chemical compounds that are toxic or harmful to cancerous cells that have the ability to rapidly grow and divide and as such these agents preferentially kill them [8–12]. These cytotoxic drugs are routinely administered intravenously in the form of free drug but failure is still being recorded especially for patients with a history of malignancies that have an allergy to chemotherapeutic agents [7,13–16]. When compared to other classes of drugs, cytotoxic drugs, lack specificity in their systemic delivery of their effects which eventually results in subsequent side effects caused by the drug attacking both healthy and target cells [17]. In addition, due to their antagonistic pharmacokinetics, there is a need to administer a high dose of the drugs. Several past types of research have shown that Fluoropyrimidines, Irinotecan, and Oxaliplatin have emerged as potent drugs of chemotherapy for CRC [18]. However, as a result of uneven and unspecific delivery into the liver [8], intestinal mucosa and other vital healthy tissues they are usually diagnosed with severe mucositis, myelosuppression, and hematological adverse reactions [19].

2. Colon cancer: causes and etiology

There are several causes of CRC, most of the CRC cases are irregular with no noticeable family history or heritable tendency. 80%–85% of CRC patients with nonhereditary sporadic adenomatous polyposis (SAP) exhibited a somatic mutation of the adenomatous polyposis Coli (APC) as a distinctive marker. Furthermore, mutation of the APC gene was earlier identified as

the cause of CRC but several factors have been recently identified as causative agents of CRC that includes diets, smoking, environmental hazards, viruses, and lifestyles of different individuals (Fig. 1) [20–25].

Currently, most of the chemotherapies are Intravenous therapy, which involves administration of chemotherapeutic agents directly into the vein, however, intravenous therapy exposes the patient to the risk of blood bacterial infection through the break of the skin [22,27–31]. In addition, intravenous therapies have not proven to be potent to treat colon cancers as the administered drugs is responsible not only for the death of cancerous cells but also the healthy and vital cells in the body, which results in very serious and life-threatening side-effects [32]. The most common treatment option for CRC is surgery that involves the removal of cancerous tissues by minimally invasive surgery followed by radiotherapy to help decrease the size of the colon cancer tumor by inducing DNA fragmentation processes and inhibits intracellular membranes thereby causing cell apoptosis [33–35]. Therefore, the design of a more potent drug delivery systems to reduce toxicity and improve on the specific delivery to the cancerous colon area is of paramount importance in the scientific community [36–40]. It should be noted that colon cancer treatment selection fully depends on the specific stage of the patient's cancer and medical history and conditions [41–45]. Over the years several polysaccharides have been demonstrated for colon-specific drug delivery Table 1. It should also be noted that in addition to polymers, other drug carriers, such as Microparticles, liposomes, solid lipid nanoparticles have also been demonstrated effectively to target the anti-cancer drug to colon tumor (Table 1). For the purpose of this review, we will

Table 1
Showing the formulation and materials investigated for colorectal cancer.

Polymer/material	Bioactive	Formulation	Remark	Reference
Chitin	Paclitaxel	Nanoparticles	The nanoparticles were hemocompatible and in vitro drug release studies showed a sustained release of PTX. Anticancer activity studies proved the toxicity of PTX-AC NPs toward colon cancer cells	[46]
Chitosan derivatives	5-aminolevulinic acid (5-ALA)	Nanoparticles of methoxy poly(ethylene glycol)-chitosan copolymer	PEG-Chito-5-ALA nanoparticles showed the superior delivery capacity of 5-ALA and phototoxicity against tumor cells. These can be photodynamic therapy of colon cancer cells	[47]
Dextran	rIL-2	Dextran/PLGA-PLA core/shell microspheres	In the subcutaneous colon carcinoma BALB/c mice models, intratumorally administrated microspheres showed better local efficacy at tumor site mediated by rIL-2 from a single dose of microspheres than that of multiple rIL-2 solution injections	[48]
Pectin	5-fluorouracil (5-FU)	Zinc pectinate pellets	In situ intracapsular wetting of pectin coat by dissolution medium resulted in the formation of ethylcellulose plug interconnecting with pellets through the binding action of pectin. Less than 25% of the drug was released in the upper gastrointestinal tract. The majority of drug was released upon prolonged dissolution and in response to colonic enzyme pectinase, which digested core pellets	[49]
Guar gum	Piroxicam	Tabletted guar gum microspheres	Crosslinked guar gum microspheres of piroxicam were directly compressed into matrix tablet and coated with Eudragit S100. The optimized tablet that displayed 0% release in simulated gastric fluid, 15% in simulated intestinal fluid and 97.1% in simulated colonic fluid underwent roentgenographic study in rabbits to check its safe transit to the colon. This could be used as targeted adjuvant therapy for colonic adenocarcinomas	[50]
Alginate	Iron-saturated bovine lactoferrin (Fe-bLf) protein	Alginate-enclosed chitosan-calcium phosphate-loaded iron-saturated bovine lactoferrin nanocarriers (Fe-bLf-loaded NCs)	After oral delivery, the pharmacokinetic and bioavailability studies indicated that nanoformulated Fe-bLf was predominantly present on tumor cells (Caco-2) compared to non-nanoformulated Fe-bLf. Fe-bLf-loaded NCs were found to help in absorption of iron	[51]
Hyaluronic acid	A near-infrared fluorescence imaging dye (Cy 5.5) and irinotecan	Poly(ethylene glycol)-conjugated hyaluronic acid nanoparticles (P-HA-NPs)	Cy5.5-P-HA-NPs and IRT-P-HA-NPs showed theranostic and therapeutic monitoring potential for colon cancer	[52]
Copolymer of 2-hydroxyethyl methacrylate with 4-methacryloyloxy Triglyceride esters	5-FU	Hydrogel	Drug release was faster and greater in human fecal media compared to simulated gastric and intestinal fluids. Faster release due to the cleavage of the azo crosslinks in the hydrogel by the azoreductase	[53]
	5-FU	Solid lipid nanoparticles by evaporation technique	SLNs system has a high potential to improve the uptake of anticancer drugs inside colon tumors. The release profile of the drug in simulated colonic medium showed a prolonged pattern that may allow spreading of the drug inside the colon to cover most of the colonic area wherever the tumors may exist	[54]

discuss the use of polymer conjugates or copolymers in the design of 5-FU delivery systems.

2.1. Delivery routes

There are several routes to achieve drug targeting to colon amongst them is direct administration from the rectum (Fig. 2) and oral route (Fig. 3). Each of these routes offers advantages and disadvantages for its use. Administration via the rectum, has shown to be effective in the rectum because of their effectiveness in spreading across the colon but limited to the sigmoid and descending colon [55].

The direct rectal administration is in its way ineffective in distributing the precise drug dose to the entire area of colon making it a non-preferred method for a drug delivery in the management of colon cancer [40].

The oral route would have been an alternative way of administering chemotherapy drugs via colon-targeted oral drug delivery systems but these drugs are mostly absorbed or broken

down in the stomach wall and small intestine prior to successful delivery of the drugs to the colon region (Fig. 2). However, knowing and understanding the chemical and physiological factors affecting drug delivery across the digestive tract can overcome this major setback [56]. The use of a selective delivery system has also been instrumental in point delivery of drugs directly to colon at high concentrations of the chemotherapeutic drug to the colon rectal region, however, there is a need to administer a reduced dose of the drug in other to decrease the occurrence of side effects [57].

2.2. 5-Fluorouracil

5-Fluorouracil (5-FU or 5-fluoro-2, 4-pyrimidinedione) is an antimetabolite of the pyrimidine analogue type, with a broad spectrum of activity against solid tumors, alone or in combination chemotherapy regimens [58]. Due to 5-FU structure, 5-FU obstructs with nucleoside metabolism and can be incorporated into RNA and DNA single and double helix respectively, thereby leading to cytotoxicity and finally cell death. 5-fluorouracil (5-FU)

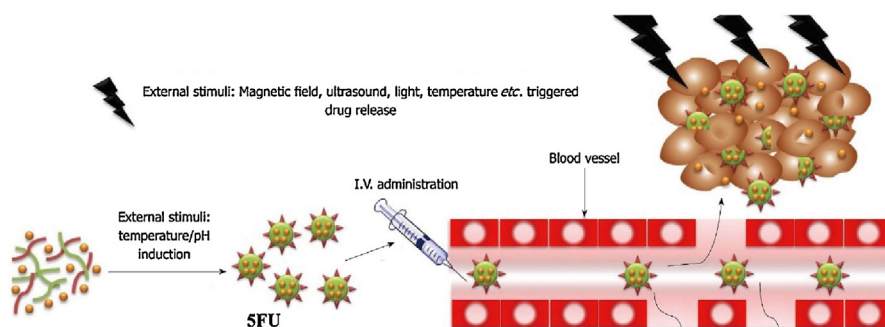


Fig. 2. Showing delivery of 5-FU via IV administration. The figure depicted the I.V. administration of 5-FU in blood vessel, which then diffuse into tumor location. This figure was.

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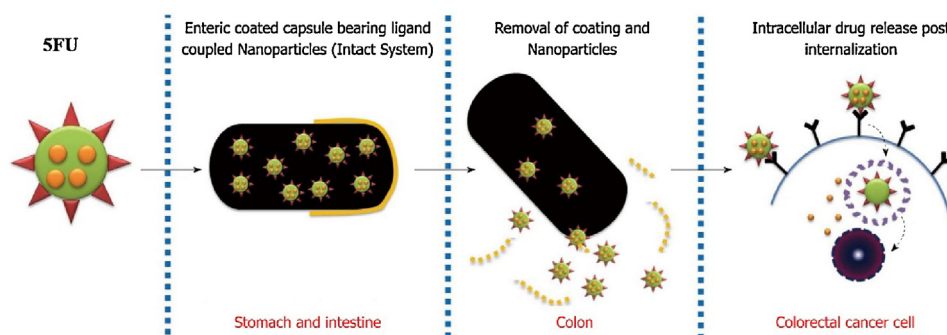


Fig. 3. Showing Oral/enteric targeted delivery of 5-FU to the colorectal cancerous cell. The figure depicted entrapment of 5-FU in a nanoparticle, which in colon the coating of nanoparticle remove and the drug release in colorectal cancer cell location This figure was.

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is considered one of the most potent chemotherapy drug agents for the treatment of CRC.

However, its efficacy has been greatly impeded by been able to be metabolized by dihydropyrimidine dehydrogenase enzyme in the gut wall immediately after oral administration [58]. The clinical application of 5-FU has not been maximally channeled as a result of the ability of tumor cells to develop drug resistance, furthermore, 5-FU chemotherapy needs/requires a continuous and regular administration of high doses because of its high rate of metabolism in the body [59]. Because of these reasons, intravenous administration of 5-FU has been preferred to oral therapy but not with its own disadvantages like severe cardiac, neural and gastrointestinal side effects.

An efficient and successful 5-FU delivery system should possess the following characteristics:

- Physical stability
- Small size
- Degradation-proof
- No low storage and drug leakage problems
- Controllable
- Biodegradability

2.3. Fluorouracil delivery systems

The following are few of the common 5-FU colloidal carriers and strategies developed for its delivery to cancer [60].

Biodegradable polymeric particles

- Hydrogels
- Vesicular systems: liposomes and niosomes
- Magnetic drug delivery systems
- Lipoproteins
- Clay minerals and anionic clays
- Metals
- Ion exchange resins

2.4. Biodegradable materials

There are several types of biodegradable materials for the application of drug delivery system based on the degradation rate of the coating materials and the delivery rate of the drug they encapsulate [61]. Poly(lactide-co-glycolide) (PLGA) is a proven and approved commonly used biomaterial. Below are the some of the biodegradable polymeric material used in 5-FU delivery to colon cancer region [62].

2.5. Alginate beads

Alginate is a copolymer of glucuronic acid and manuronic acid and its usefulness is harnessed in both the drug and pharmaceutical industry. The ability of sodium alginate to form a gel formation in the presence of Ca^{2+} ion ability has been harnessed in the aspect of drug delivery. 5-FU is coated with alginate beads of a diameter of about 1–2 mm through the process of gelation of alginate with calcium cations. The alginate beads are prepared by the process of extrusion [63].

The alginate coated 5-FU beads are hydrophilic drug and their coating efficiencies is about 10% and the researchers reported that the increase in the drug-load is proportional to the size of the beads obtained, in which the resulting beads have an increased number of 5-FU. Finally, it was reported that the number of 5-FU released from beads is inversely proportional to alginate concentrations [64].

2.6. Poly(*E*-caprolactone) (PCL)

It is a non-toxic, highly hydrophobic polymer when compared to alginate polymer with a reduced rate of degradation and it's important in both in vitro and in vivo culture medium and it has been used over the years for 5-FU delivery systems for cancer treatment [65]. Poly-*e*-caprolactone has been used as implantable-loaded matrices with 5-FU. The biodegradable block was made by reacting PCL block with poly(ethylene glycol) block without any reactive catalyst at a temperature of about 185 °C [66]. This copolymer structure was formed through a known ring-opening procedure, which uses an active hydrogen atom of the poly(ethylene glycol) block and then causes a selective acyl-oxygen cleavage of an ester group of the monomer ring. The report of these scientists has shown that there is a possibility of using PCL as a "time-delayed" 5-FU releasing system: a fast release of the anticancer drug in the first 10 h is followed by a slow release phase, and finally reaches a limiting value after 24 h [67].

2.7. EUDRAGIT[®]

Eudragit drug delivery system uses the principle of the pH-sensitive approaches like methacrylate/methacryl acid polymers Eudragit[®] S and L in a slightly acidic to neutral aqueous media at pH 6 and 7. Furthermore, there has been elaborate and extensive research works on Eudragit[®] P-4135F and Eudragit[®] RS100 on microencapsulation of 5-FU in the oral treatment of colon cancer and Eudragit[®] RS100 has been proven efficient for matrices spray-coating when used for the colorectal carcinoma treatment (Fig. 4). Eudragit[®] P-4135F a pH-sensitive drug, through the process of oil/water emulsification has been used to develop 5-FU-loaded microspheres, through this method, the microparticles made from Eudragit[®] RS100 within 8 h of administration, 5-FU was delivered

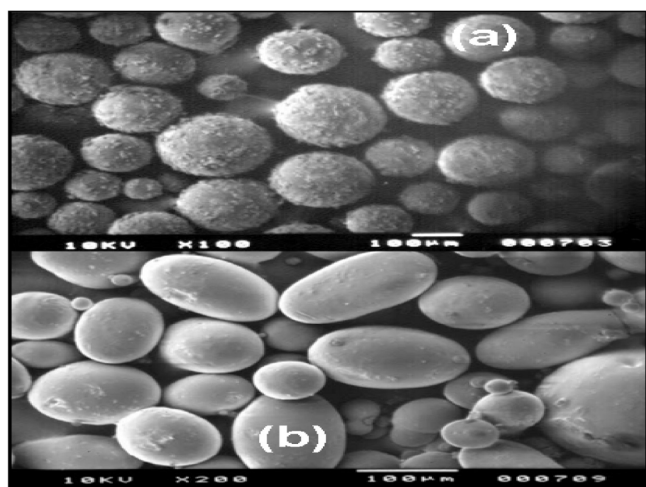


Fig. 4. SEM images of microspheres prepared with Eudragit[®] P-4135F (a) and Eudragit[®] (b) using an oil/oil emulsification process. This figure was reproduced with permission from [71]. Eudragit[®] has been proven efficient for matrices spray-coating when used for the colorectal carcinoma treatment.

to the colon region. Past research studies on in vitro drug release have elucidated more on the application of a designed microspheres of 5-FU using a mixture of Eudragit[®] P-4135F and Eudragit[®] RS 100. for the delivery of 5-FU in the treatment of colon cancer tissue. Invitro and in vivo research data from past works have established that when 5-FU loaded with Eudragit[®] S100 and coated with calcium pectinate beads is orally administered, it delivers its load accurately to the colon [68].

Rahman Z et al. [69] reported a delivery system that employs the use of pH and bacteria trigger mechanism that uses Eudragit[®] S100 as a coating for alginate microspheres containing 5-FU. It was found effective in targeting the colon cancer tissue in a rat model and with minimal systemic side effects. The Eudragit[®] S100 coating has a protective function over the microspheres as it transits via the digestive system prior to degradation in the colon and exposing the alginate core to colonic bacteria for digestion (Fig. 5).

Zambito Y et al. reported that controllable 5-FU designed matrices are effective for the oral delivery system to treat and manage colon cancer tissue. The matrices with a diameter of 0.6mm coated with 5-FU were designed to be placed within an enteric coated capsule for a specific targeting of the drug to the colon in addition the matrices were also coated with a protective Eudragit[®]S100 film and covered in a layer of chitosan hydrochloride. Which is responsible for dissolution and controlled the release of 5-FU in the physiological environment of the colon [70].

2.8. Guar gum

Guar gum is a polysaccharide derived from *Cyamopsis tetragonolobus* (*Leguminosae* family). Developed for site-specific delivery of 5-FU to the colon by Krishnaiah et al., 80% of guar gum in compression-coated tablets have high efficient of delivery 5-FU successfully to a colorectal region. It remains a potential carrier for colon-specific drug delivery, delivery by guar gum shows no changes in physical appearance or dissolution pattern. Also, majority of the 5-FU load was delivered directly into the human colon with minimal to zero amount of the drug residue in the intestine when a delivery system that employs the use of a 5-FU

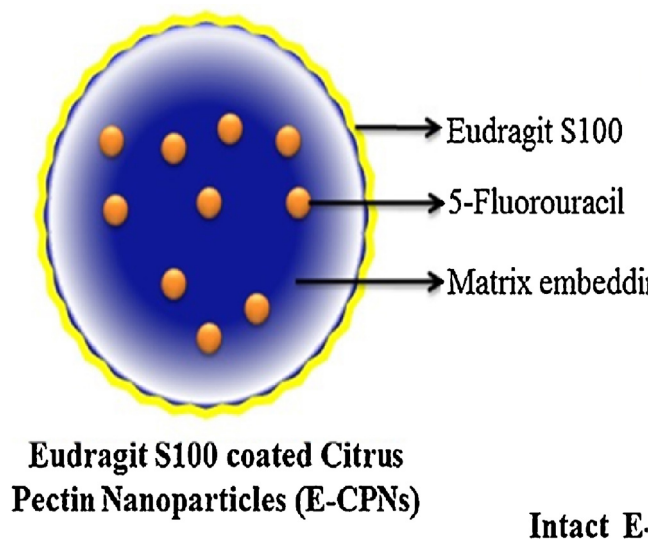


Fig. 5. Schematic structure of Eudragit S100 coated Citrus Pectin Nanoparticles (E-CPNs), which loaded 5-Fluorouracil. The coating has a protective function over the microspheres as it transits via the digestive system prior to degradation in the colon and exposing the alginate core to colonic bacteria for digestion.

guar gum compression-coated formulations was used. In regards to this previous study, other scientists have focused on this the area by using a combination of various polysaccharide gum as a compression coat over the core tablet for a controllable delivery system of 5-FU [72].

3. Bovine serum albumin (BSA) nanoparticle

Ghazal Fadaeian and colleagues have demonstrated the delivery efficiency of anti-HER2 mAb-coupled BSA nanoparticles loaded with an anticancer drug, 5-FU. They reported that this targeted delivery system was able to improve the therapeutic effect of 5-FU on HER2-positive cells. The combination of specific targeting with drug loading in these HSA based nanoparticulate systems should lead to an improvement in cancer therapy (Fig. 6) [73].

3.1. Poly(D,L-lactide) (PLA) and poly(D,L-lactide-co-glycolide) (PLGA)

Poly(D,L-lactide-co-glycolide) (PLGA) and poly(D,L-lactide) (PLA) are the most commonly and highly preferred biodegradable material because of biocompatibility and biodegradability properties they possess. The by-product of the breakdown of PLA and PLGA through the process of hydrolysis are lactic and glycolic acids and are finally removed as citric acid. The process of emulsification and solvent evaporation are two processes involved in the preparation of PLA and PLGA nanoparticles. Poly(D,L-lactide) (PLA) polymer is under investigation for the design of novel block copolymer loaded with 5-FU.

Several researchers have developed several nanoparticles that have pH-responsive and biodegradable properties that work on the principle of grafting biodegradable PLA onto *N* isopropylacrylamide and methacrylic acid. The most commonly used method is the preparation of PLA-PEG-PLA triblock copolymers. Several techniques have been developed to maximize 5-FU loading to PLA nanoparticles amongst them are [74]:

- Oil-in-oil emulsion solvent evaporation technique
- Nanoprecipitation-solvent displacement technique
- A triphasic release technique

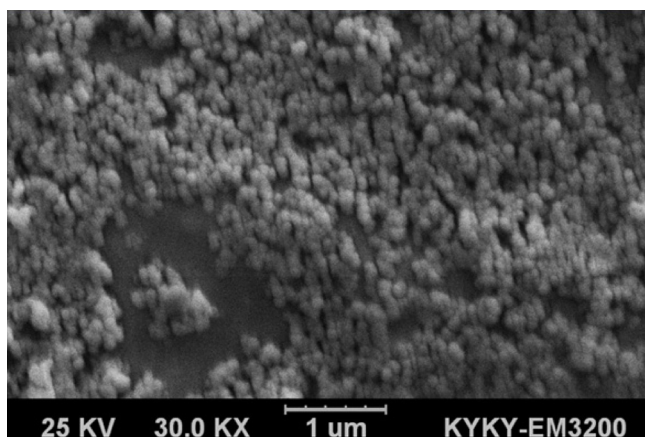


Fig. 6. SEM micrograph of 1F2-coupled 5-FU-loaded BSA nanoparticles at 30000X magnification. This figure was reproduced with permission from [73].

4. Preclinical research studies with 5-fluorouracil delivery systems

At present, several drugs are available for the management of CRC. 5-Fluorouracil (5-FU)/Leucovorin is the first-line treatment, and the most common chemotherapy for metastatic CRC by inhibiting thymidylate synthase. 5-fluorouracil (5-FU), combined with leucovorin as been identified as a potent systemic chemotherapy treatment for colon cancer. Presently 5-FU is administered given as an intravenous injection and is directly delivered into tumors, gut mucosa, bone marrow, and hepatic tissue as uracil. 5-FU effects its action by blocking the synthesis and the action of the thymine nucleotides and the enzyme thymidylate synthase respectively [75]. In addition, 5-FU also undergo bioinactivation by a liver enzyme called dihydrouracil dehydrogenase, however, bioactivation of 5-FU-5-uoro-2'-deoxyuridine occurs mostly in colon cancer cases than in healthy tissue. The activity of this enzyme has been recorded as highest and lowest in the liver and colon respectively. If 5-FU is delivered specifically/directly to the colon infected region, the active metabolite of 5-FU(5-uoro-2'-deoxyuridine) should be most available in colon tumor and the systemic side effects of 5-FU associated with the intravenous administration will be minimized.

5. Delivery system

Colon targeted oral delivery system is one of many logical approaches in using chemotherapy as a treatment option for colon cancer of any stage as it is able to provide both systemic and regional delivery of 5-FU, oxaliplatin, capecitabine and irinotecan. This hypothesis has been based on the ability of the colon acting as a possible site for systemic and local drug delivery [76]. In order to develop a colon-targeted oral drug delivery system in the treatment and prevention of colon cancer, it's of importance to take note of the site of action and mode of action of 5-FU given that 5-FU is well delivered into the intestinal mucosa, bone marrow, liver after been administered intravenously as uracil. To overcome the challenges of adverse side effects posed by chemotherapy, oral drug delivery systems has been developed to transport the therapeutic drugs from gastrointestinal tract to the colon area. The oral drug delivery systems can achieve the sustained drug release using the biodegradable encapsulation materials. This also enables the drug delivery carriers to be compatible with the human body. In order to reduce both systemic side effects and dose/duration of CRC therapy, a precise-specific and dose/rate controlled delivery system must be adopted [74].

Several studies have reported some new approaches on the development of colon-targeted oral 5-FU delivery systems namely such as:

A new research based on pluronic block copolymers with multiple effects was reported to be potent as a drug delivery system. In the report, a new co-delivery system, pluronic P85 block copolymers, responsible for delivering chemotherapeutic agent 5-Fu, one of the anticancer agents used in the treatment of colon cancer and another form of cancer, was developed in order to reinforce the drug curative effect.

Similarly Xu C, et al. [77] reported that the efficacy of pectin and its salts in an in vivo study as a carrier for colon-specific drug delivery, this further proves right earlier studies on the potency of pectin and calcium pectinate as carriers for colon-specific drug delivery. In another study, a pectin based colon specific delivery system was used and the delivery of the 5-FU into the stomach and digestive system was minimized by an enteric coating. Several studies on in vitro drug release and in vivo organ distribution have shown the efficacy of enteric-coated pectin microspheres to deliver 5-FU to the colon. Studies in rat model have also proven the

efficacy of 5-FU pectin conjugate covalently synthesized and distributed in vivo. All these results further corroborate earlier suggestions about the specific location of 5-FU-pectin conjugate in the digestive system- the caecum and colon.

In in vitro study done by Wei H, et al., he reported that when pectin and ethyl cellulose in the ratio of 1:2 at a film thickness of 20% of the total weight is coated with 5-FU, the effectiveness of the drug release into the digestive system is reduced, when compared to a more effective and satisfactory drug release at a film thickness of about 30% of the total weight as most of the coated pellets moves rapidly via the digestive system and reaches the colon 4 h later [71]. It took a longer time after oral administration of the coated pellets, for the 5-FU to appear in the plasma and reached a reduced peak plasma concentration. However, the plasma concentration for uncoated pellets was recorded higher than the coated pellet and took a longer time to appear in the plasma, thereby suggesting that pectin and ethylcellulose (1:2) coated pellets at 30% thickness of total weight gain can deliver 5-FU to colon for local action.

Lamprecht A et al. combined 5-FU and leucovorin by microencapsulation using sensitive polymers, given leucovorin is a promoter factor for the activity of 5-FU for delivery in distal colon [71]. In another study, a multiparticulate technique was used as an oral-delivery system that employs the use of a lectin-conjugated Chitosan-Ca-alginate microparticles loaded with acid-resistant particles for potential treatment of colon cancer tissue. Hydrogels, a product of modification of psyllium with acrylic acid with a responsive pH has been proven to be potent for 5-FU delivery to the colon. Oral Consumption of psyllium has the efficacy to reduce the risk of colon cancer in humans as such it has a dual pivotal role by delivery and itself acting as an anticancer therapeutic agent [78].

6. Conclusion

Unfortunately, current chemotherapeutic treatment for colon cancer administers high doses of cytotoxic drugs, specifically combinations of 5-FU and Irinotecan, which leaves the patient with serious health side effects. It is necessary to develop new nanomedicines with multifunctional abilities that work on the principle of different chemotherapeutic agents; with reduced systemic doses and ultimately reducing the risk of serious health side effects. Furthermore, concomitant research approaches aimed at overcoming the rapid metabolism and drug resistance associated with 5-FU should be developed. Although several of these delivery approaches developed for 5-FU has led to an efficient improvement in the management and treatment of cancers at the preclinical stage, however, more studies are still needed to better define potency and establish their efficiency in clinical practice. Finally, more research on physicochemical and preclinical studies is still needed to investigate more on the development of surface-functionalized delivery systems for 5-FU with more efficient and specific delivery of 5-FU at the colon cancer region and able to improve on the 5-FU uptake by cancer cells.

Declaration of interest

The authors have no declaration of interest. The authors alone are responsible for the content and writing of the paper.

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