MINI-REVIEW

New Approaches to Use Nanoparticles for Treatment of Colorectal Cancer; A Brief Review

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ABSTRACT

Nanoparticles have been at the center of research focus as a new promising material for the treatment of cancer in recent years. Although many chemotherapy drugs for cancer treatment are available, their potential toxicity is the main point of concern. On the other hand, the conventional chemotherapeutic approach has not been found to be very efficient in colorectal cancer (CRC) as the drug molecule does not reach the target site with an effective concentration. A major challenge in cancer therapy is to destroy tumor cells without harming the normal tissue. To overcome this problem scientists are trying to use nanoparticles to directly target cancer cells for a more effective treatment and reduced toxicity. Different nanoparticles such as: liposomes, polymeric nanoparticles, dendrimers, and silica have been developed to carry a variety of anticancer agents including: cytotoxic drugs, chemo modulators, siRNA and antiangiogenic agents. This review discusses various treatments for colon cancer and the potential use of nanoparticles which facilitate targeting of cancer cells. The outlook for new treatment strategies in CRC management is also underlined.

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INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of cancer death the U.S. and additionally the third widely diagnosed cancer in the world [1]. CRC survival is greatly dependent on the stage of the disease and usually ranges from a 90% 5-year survival rate for cancers detected at the localized stage to 10% of people diagnosed for distant metastatic cancer. The earlier the stage of diagnosis, the higher the chance of survival [2]. Currently there are many various therapies for CRC which include surgery, chemotherapy, and radiation therapy. However, these procedures are not very efficient as the drug reaches the target site in non-effective concentrations. However, higher dose may lead to adverse effects [3]. Nanoparticles, of which at least one dimension is smaller than 100 nm, have a great potential in drug delivery and clinical therapeutics and are important for applications in cancer drug delivery [4-6]. There are key advantages of nanoparticle drug delivery including longer circulation half-lives, improved pharmacokinetics, being capable of carrying a large amount of drugs, decreasing side effects and targeting the drug to a specific location in the

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Table 1. Some of the main advantages and disadvantages of routine nanoparticles

Nanoparticle	Advantage	Disadvantage
Liposomes	-Increased efficacy and therapeutic index of drug (actinomycin-D) and stability via encapsulation -Non-toxic, flexible, biocompatible, completely biodegradable, and non-immunogenic for systemic and non-systemic administrations -Decrease the exposure of sensitive tissues to toxic drugs [9]	-Low solubility -Short half-life -Leakage and fusion of encapsulated drug/molecules -high cost -Fewer stables [10]
Polymers	-Stability of any volatile pharmaceutical agents -delivers a higher concentration of pharmaceutical agent to a desired location -easily merged into other activities associated to drug delivery [10]	-Noxious factors such as toxic, reactive residues, unreacted monomers, the risk of a chemical reaction and the formation of unwanted oligomers [11]
Dendrimers	-Lower polydispersity index [12] -Outer surface of dendrimers has multiple functional groups -they can be synthesized and designed for specific applications [13] -assemblies such as DNA and proteins [14]	Insufficient loading capacity, drug expulsion after polymorphic transition during storage [15]
Silica	-Their unique properties amenable for *in vivo* application versatility, non-toxicity, biocompatibility, biodegradability [16, 17]	-Expensive [18] -The skeletal stability of liposomes is very low and is further lowered during fluid sheer stress which can occur during circulation [16]
Nanoemulsion	-Substitute for liposomes and vesicles [19] -Bioavailability of drug -Non-toxic and non-irritant in nature -greater absorption [20]	-The surfactant must benon-toxic for using pharmaceutical application [21] -Stability influenced by environment parameters such as temperature and PH - High concentrations of surfactant and co-surfactant are important for sustaining the nano droplets [22]

body (Table 1)[7, 8]. This article briefly reviews the nanoparticle-assisted co-delivery of drugs for CRC therapy.

Drug delivery system with nanoparticles

Nanoparticle drug delivery platforms have been in center of focus of researchers. Many solid tumors such as breast, lung, prostate, and colon cancers have unique structural features including the hyper permeable vasculature and impaired lymphatic drainage, hence, tumor tissues are quite permeable to macromolecules and nanocarriers [23, 24]. There are two major mechanisms for cell-specific targeting with nanocarriers: active and passive. The first strategy depends on the interaction between the nanocarriers and receptors on the target cell. Passive targeting involves mechanisms to increase vascular permeability and also to retain long-circulating nanocarriers at tumor sites in their flow to impaired lymphatic system [25]. Enhanced permeability and retention (EPR) effect, nanoparticle clearance by the mononuclear phagocyte system (MPS), and desirable nanoparticle characteristics for cancer applications are important concepts in nanoparticle drug delivery. The EPR effect has a critical role in determining the efficacy of the nanoparticle-based drug delivery system [26]. There is however, a common problem among nanoparticles where they are quickly absorbed by macrophages, so-called MPS. The MPS (also known as the Reticulo Endothelial System (RES)) is mostly responsible for clearing macromolecules from circulation [27]. One of the major programs

Table 2. Liposomal drugs in targeting tumor cell

Drug	Brand name	Acts in the cancer cell	Circulation time	Stage	Cancer(s)	Ref.
Doxorubicin	Doxil®	1) Intercalation into DNA and poisoning of topoisomerase-II-mediated DNA repair (TOP2A) 2) Generation of free radicals and causing cellular membranes, DNA and proteins damage	350 hours	FDA approved	Ovarian Cancer Solid Tumors Bladder Cancer Lymphoma	[45]
Vincristine	Marqibo®	Binds to tubulin causing microtubule depolymerization, metaphase arrest and apoptotic death of cells undergoing mitosis	6.6 hours	FDA approved	Colorectal Cancer, Acute Lymphoblastic Leukemia (ALL), Sarcoma, Neuroblastoma, Wilms Tumor, Leukemia, Lymphoma, Brain Tumors and other tumors	[46]
Doxorubicin	Thermodox®	1) EPR** effect 2) When heated, blood vessels in tumors become even more permeable, further increasing the accumulation of liposomes in tumors before releasing the drug payload	NI*	Phase II clinical trial	Colon Cancer with Liver Metastasis	[47]

*NI: No information
**Enhanced permeability and retention (EPR)

to prevent the rapid RES uptake is coating of the particles with surfactants or covalent linkage of polyoxyethylene [27, 28]. There a re d ifferent characteristics for delivering conventional therapeutics to solid tumors; life-size (less than 200nm), spherical shape and a smooth texture. Although particles larger than 500 nm are rapidly eliminated from the circulation [29].

Liposomes

In 1961, Bangham described liposomes as the first n anoparticle p latform a pplied i n m edicine [30]. Liposomes were the first d rug-delivery system approved for clinical purposes. One of the most used delivery systems for small molecules, peptides, small and long nucleic acids, and proteins are liposomes and particularly nanoliposomes [31]. Liposomes are small, spherical artificial carriers with an aqueous core and are naturally non-toxic [32]. Due to their phospholipid bilayer, their size and their ability to incorporate various substances liposomes are the most effective drug delivery systems into cells with slow-releasing and targeting characteristics and the ability to decrease side effects [33, 34].

Liposomes according to their different properties are divided into 3 groups:

1) Long-circulating liposomes (stealth liposomes): The conventional liposome surface is strongly affected by opsonization and the opsonized liposomes are subjected to uptake by MPS and subsequent clearance. Phospholipid bilayer structure of the liposome is modified by adding gangliosides or a polyethylene glycol (PEG) which tends to avoid blood plasma opsonins binding to the liposome surface. Subsequently, PEG causes

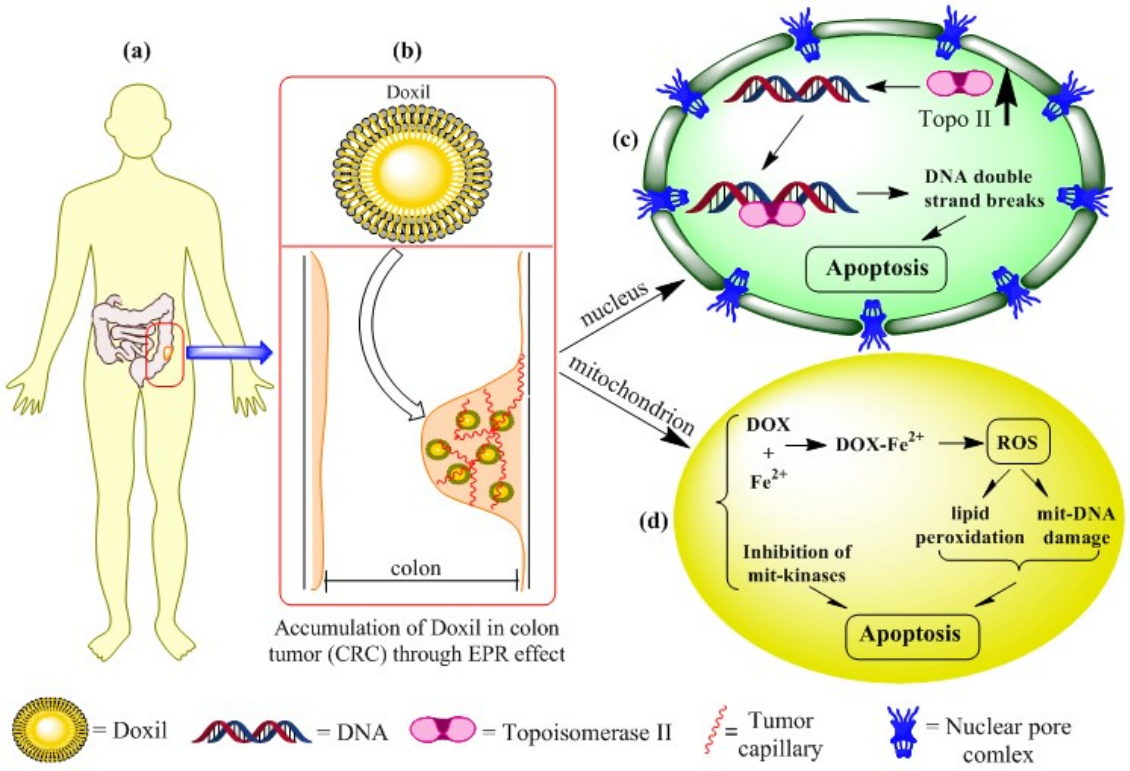

Fig. 1. schematic illustration of colorectal cancer and Doxil mechanisms, (a) colorectal cancer, (b) accumulation of Doxil in colon tumor, (c) molecular mechanism of Doxil in the nucleus, increase of topoisomerase II, induced by Doxil, causes more DNA breaking which subsequently leads to apoptosis, (d) molecular mechanism of Doxil in the mitochondria, Fe2+-conjugated Doxil causes ROS production which consequently induces apoptosis. On the other hand, Doxil inhibites the mitochondrial kinases, resulting in apoptosis induction.

a decrease in recognition of liposomes by the mononuclear phagocyte system and enables liposomes to stay stable in the circulation and maintain a prolonged half-life [35-37];

2) Active targeting liposomes: Liposomes targeting antibodies, glycoside residues, receptors, hormones and peptides;

3) Liposomes with special properties include thermo-sensitive, pH-sensitive, magnetic and positive;

Liposome formulation carrying the chemotherapeutic drug such as Doxorubicin (Doxil®) and daunorubicin (DaunoXome®) has been approved by FDA since the mid-1990s [38]. Doxil is approximately 100 nm and has much less cardiac and gastrointestinal toxicity although many side effects such as: redness, tenderness, and peeling of the skin which can be painful [39] can still be seen. The most recent liposomal drug, which has been approved by FDA since 2012, is Marqibo® (Fig. 1) [40-42]. Marqibo is about 100 nm and cell cycle-dependent anticancer drug. There have been some efforts to fight drug resistance such as the results obtained when administrating liposome-based like Doxorubicin. Li *et al*. have determined that when administering high dosages of a carrier for the antitumor drug Doxorubicin (DOX); such as L33, an aptamer-based drug delivery system, has the conceivability to conduct high dosages of the drug towards the target cells (Fig. 2) [43]. Thermodox® (also known as thermo-sensitive liposome Doxorubicin) is another example which is in Phase II trials for colorectal liver metastases in combination with RFA (radiofrequency ablation). It is a liposomal Doxorubicin formulation that releases the drug in response to a mild hyperthermic trigger (Fig. 3) [44]. Thermodox has been shown to deliver 25 fold more Doxorubicin into tumors than IV Doxorubicin does and fivefold more Doxorubicin than standard liposomal formulations of the drug in animal models (Table 2).

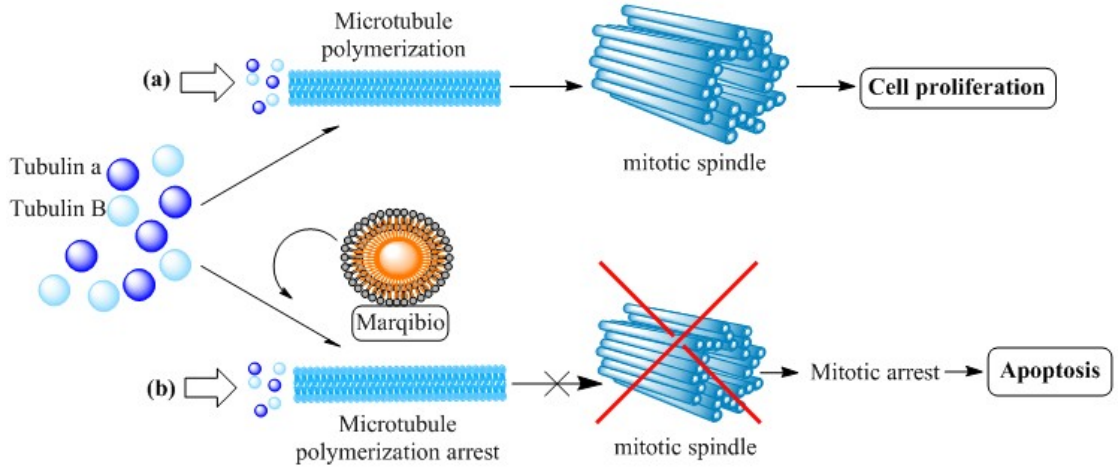

Fig. 2. The effect of Marqibio on microtubule polymerization, (a) cell proliferation in the absence of Marqibio, (b) inhibition of microtubule polymerization in the presence of Marqibio which consequently leads to apoptosis.

Polymeric nanoparticles

Polymeric nanoparticles (PNPs) or synthetic polymers are structures with a diameter between 10 to 100 nm. The PNPs are mostly covered with nonionic surfactants to decrease immunological interactions (e.g. opsonization) [48, 49]. Poly lacticco-glycolic acid (PLGA) and polycaprolactone (PCL) are two main examples of PNPs which have been approved by the US FDA [50]. 5 fluorouracil (5-FU) is the first-line therapy for CRC, however in practice, the healthy cells are also affected when administered and on the other hand, the drug availability is not great in the colon region. Subudhi *et al.* have chosen citrus pectin and Eudragit S100 (pH-responsive enteric polymer) to use as nanoparticle drug delivery systems for site-specific delivery of 5-FU for the effective treatment of CRC [51]. They concluded that Pectin was a good carrier material in the colon-specific drug delivery systems. Safety and effectiveness of Eudragit S100 coated CPNs (E-CPNs) to deliver 5-FU in CRC both *in vitro* and *in vivo* studies have also been shown[51, 52]. Eudragit S-100 is used for coating solid dosage and does not degrade below pH 7. The main purpose of using Eudragit S-100 was to prevent quick drug release in GI system rather than the target site (colon) [53, 54]. Citrus pectin is over-expressed acts as a ligand for galectin-3 receptors on CRC cells (Table 3) [55].

Dendrimer Nanocarriers

Dendrimers are soluble in water due to having the hydrophilic functional groups [14]. Drugs can be reached interior spaces through covalent or electrostatic bonding encapsulation which are used as drug delivery vehicles. A dendrimer is one of the most elegant nanotechnology platforms for targeted drug delivery [58]. The first polyamide amine (PAMAM) dendrimers were described by Tomalia *et al.* in 1985 [59]. Because of their hyper branched structure, dendrimers often have open cavities between adjacent branches, so can allow encapsulation of drugs [60]. Dendrimers, such as poly ethyleneimine and PAMAM dendrimers, have also been examined as gene carriers because of having a positive surface [61]. Mignani *et al.* have shown that dendrimer–DOX was >10 times less toxic than plain DOX after exposure for 72 h in cell culture (C-26 colon carcinoma cells). Administration of dendrimer–DOX to BALB/c mice (bearing C-26 colon carcinoma tumors) resulted in a tumor uptake 9 times higher than plain DOX at 48 h with a half-life of 16 h. A single injection of dendrimer–DOX was quite effective where the survival of mice over two months was 100% [62].

Silica Nanoparticles

Silica materials are classified as xerogels and mesoporous silica nanoparticles (MSNs). There are several advantages: as carrier systems, including biocompatibility, highly porous framework and easy functionalization [63, 64]. Mesoporous silica nanoparticles with a porous structure like a hive of bees, which are capable of loading large amounts of various bioactive molecules. Important properties of mesoporous silica nanoparticles are as follows: A) Adjustable size of the nanoparticles and their

Table 3. Nanoparticle dugs in clinical trials

Material	Drug	Aim of study	Result	Status	Ref.
Liposomal	Liposome-encapsulated irinotecan hydrochloride PEP02	A Randomized Phase II Study of PEP02 or Irinotecan in Combination With Leucovorin and 5-Fluorouracil in Second Line Therapy of MetastaticColorectal Cancer	-To assess the objective response rates -To determine the safety, progression-free survival, overall survival in these patients	Phase 2 (has been terminated)	[56]
	SN-38 liposome	Liposomal SN-38 in Treating Patients With Metastatic Colorectal Cancer	Assess the objective response rate following treatment with SN-38 liposome as a second-line treatment in patients with metastatic colorectal cancer Determine the toxicity, progression-free survival and overall survival for patients.	Phase 2 (has been terminated)	
Polymer	5-fluorouracil (5-FU) plus a DAVANAT (carbohydrate polymer)	A New Agent GM-CT-01 in Combination With 5-FU, Avastin and Leucovorin in Subjects With Colorectal Cancer	To estimate the safety of the DAVANAT®/5-FU, LV plus Avastin® regimen	Phase 2 (has been terminated)	[57]
	Dual-surface-functionalized (Pluronic F127 and chitosan) CPT-loaded PLGA nanoparticle (NP-P/C)	Inhibiting multi-drug resistant gene 1 (MDR1) expression and enhancing tumor uptake	NPs-P/C1 exhibited the highest efficacy against subcutaneous colon tumors in mice compared with free CPT, NPs-PVA and NPs-P	In vivo (mice) /in vitro	

cavities in the range of 50 to 300 and 2 to 6 nm, respectively [44].

B) Very low toxicity, easy endocytosis, the ability of extensive loading of the drug

C) Resistance to heat and pH [65].

Radhakrishnan *et al.* used mesoporous silica nanoparticle (MSN) -protamine hybrid system (MSN–PRM) to selectively release the drugs in the proximity of cancer cells where specific enzymes can trigger the drug activity [66]. Drug-induced cell death in CRC cells was also significantly enhanced when the hydrophobic drug was encapsulated in the MSN–PRM system in comparison to the free drug ($P< 0.05$) [66]. Yu M *et al.* showed that conjugation of hyaluronic acid to MSNs, the amount of DOX loading into HA-MSNs increases than bare MSNs [67]. Cellular uptake of DOX-HA-MSNs was also increased and was shown that DOX-HA-MSNs more cytotoxicity to HCT-116 cell lines (human colon carcinoma) than free DOX [46]. In another work, Hanafi-Bojd *et al.* showed that when MSNs were functionalized with polyethylene glycol (PEG) and polyethylenimine-polyethylene glycol (PEI-PEG) groups, the amount of Epirubicin hydrochloride (EPI) loading into MSN was increased and produced an improved antitumor efficiency. The antitumor activity in C-26 colon carcinoma model was higher due to enhanced accumulation of MSN-PEI-PEG-EPI compared to free EPI [68].

Nanoemulsion system

Nanoemulsion is a transparent solution including water, oil and surfactant with thermodynamically stable and uniform physical properties. Important features of nanoemulsion are as follows: a) facilitate the process of transferring drugs and drug combinations protect against external factors (such as heat, pH) [48] b) high stability, low toxicity and efficiency and finally c)

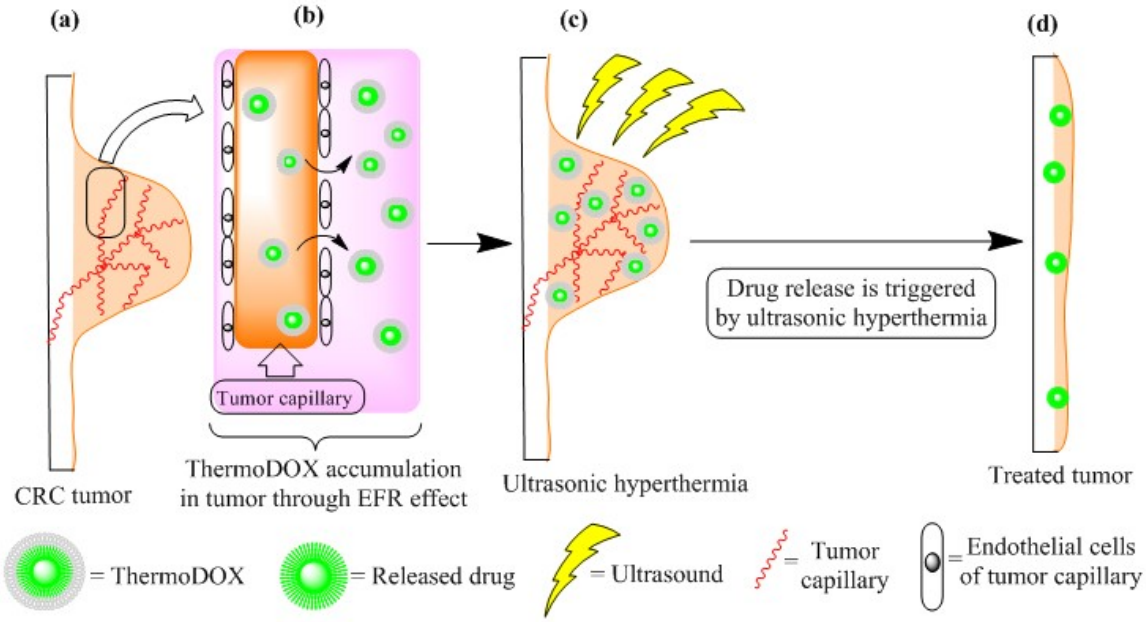

Fig. 3. the schematic diagram of the mechanism of Thermodox in colorectal cancer (CRC), (a) CRC tumor, (b) the enhanced penetration and retention (EPR) effect, (c) local hyperthermia, induced by ultrasound waves, causes drug release from the Thermodox formulation, (d) treated tumor

the ability to dissolve non-polar compounds (33). Huang *et al.* examined the synergistic effect of lycopene (LP) and gold nanoparticles (AuNPs) on HT-29 colon cancer cell line. The first case involves a system of nanoemulsion containing Tween 80 as emulsifier, LP and AuNPs and the latter includes using a mixture of LP and AuNPs without the emulsion. The nano-emulsion system, the amount of gold nanoparticles and lycopene are as follows: 0.16 ppm and 0.4μM. Also, the combination of gold nanoparticles and lycopene include doses of 10 ppm and 12μM, respectively. The final results showed that although dose of LP and AuNPs in nano-emulsion system were 250 and 125 times respectively less than the mixture mode, the apoptosis induced by nano-emulsion was three times greater than the mixture mode [69].

Core-shell polymeric NPs

There has been an increasing interest in synthesizing core/shell nanoparticles which are composed of two or more materials [70]. The core/shell nanoparticles can have different combinations including inorganic/inorganic, inorganic/organic, organic/inorganic, and organic/organic materials [71]. There are different purposes of coating on core particles with an important factor being surface modification. Many other purposes include: increasing the functionality, stability and dispersibility of the core particles. Furthermore this also gives a controlled release of the core and a reduction in the consumption of precious materials [72]. They have different applications in biomedical field for instance: controlled drug delivery, for bio-imaging, for cell labeling, and in tissue engineering applications [73-75].

Combined anticancer therapies loaded in NPs for colon cancer therapy

Combination of Drug-loaded Nanostructures in the treatment of CRC shows potential to enhance local drug concentration, improving chemotherapy and tumor-targeting [76]. Anita *et al.* examined the anticancer effects of curcumin/5-fluorouracil loaded thiolated chitosan nanoparticles (Cur-TCS/5-FU-TCS Nanoparticles) on colon cancer cell line (HT29). Nanostructures of Cur-TCS (size = 150 nm and zeta potential = + 35mV) and 5-FU-TCS (size = 150 nm and zeta potential = +48mV), which are sensitive to pH, were also compared as freely used, and had2 and 3-fold increase in anticancer effects. The amount of necessary dose to view a specific cytotoxic effect was also reduced [77]. Payjakata *et al.* designed pH-sensitive

polymer nanostructures which carries curcumin. In this process, the drug encapsulation efficiency was 72% and the particle size less than 130 nm. These nanostructures could be used to reduce the dose of curcumin to inhibit colon cancer as well as increasing the cellular uptake of curcumin [78].

CONCLUSIONS

Nanoparticles are on the edge of medical research at present. Nanosystems in therapies for diseases have been in the center of focus as a new material to achieve an effective cancer treatment. The combination of drug molecules with nanocarriers can protect it against degradation and also offers the possibilities of targeting and controlled release. Nanocarriers are able to cross the blood-brain-barrier (BBB) and operate at the cellular level. Some nanoparticles are approved by the US FDA at present; several others are presently under development and clinical assessment. Nanoparticle platforms have provided an opportunity to develop techniques in drug conjugations and nanomaterials engineering for better therapeutic regimens.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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