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)

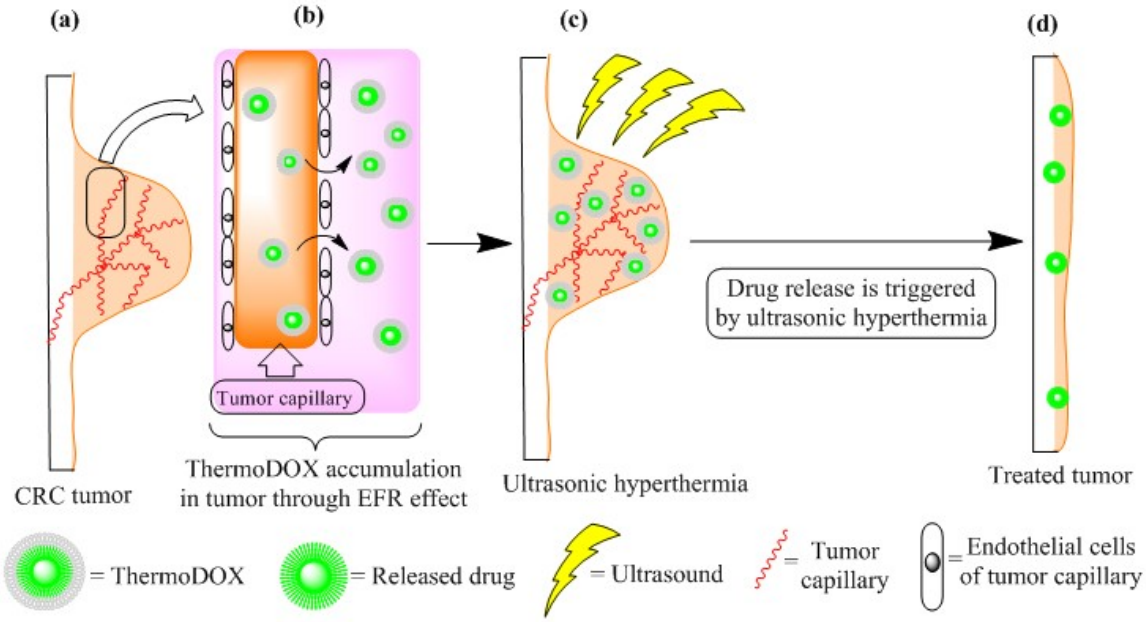

Fig. 3. the schematic diagram of the mechanism of Thermodox in colorectal cancer (CRC), (a) CRC tumor, (b) the enhanced penetration and retention (EPR) effect, (c) local hyperthermia, induced by ultrasound waves, causes drug release from the Thermodox formulation, (d) treated tumor

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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