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Review article

Doxorubicin-loaded micelles in tumor cell-specific chemotherapy

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ABSTRACT

Nanomedicine is a field that combines biology and engineering to improve disease treatment, particularly in cancer therapy. One of the promising techniques utilized in this area is the use of micelles, which are nanoscale delivery systems that are known for their simple preparation, high biocompatibility, small particle size, and the ability to be functionalized. A commonly employed chemotherapy drug, Doxorubicin (DOX), is an effective inhibitor of topoisomerase II that prevents DNA replication in cancer cells. However, its efficacy is frequently limited by resistance resulting from various factors, including increased activity of drug efflux transporters, heightened oncogenic factors, and lack of targeted delivery. This review aims to highlight the potential of micelles as new nanocarriers for delivering DOX and to examine the challenges involved with employing chemotherapy to treat cancer. Micelles that respond to changes in pH, redox, and light are known as stimuli-responsive micelles, which can improve the targeted delivery of DOX and its cytotoxicity by facilitating its uptake in tumor cells. Additionally, micelles can be utilized to administer a combination of DOX and other drugs and genes to overcome drug resistance mechanisms and improve tumor suppression. Furthermore, micelles can be used in phototherapy, both photodynamic and photothermal, to promote cell death and increase DOX sensitivity in human cancers. Finally, the alteration of micelle surfaces with ligands can further enhance their targeted delivery for cancer suppression.

1. Introduction

Doxorubicin (DOX) is a routinely prescribed antitumor drug in cancer treatment (Al-Malky and Al HarthiA.-M.M.J.J.o.O.P.P. Osman, 2020). DOX has anticancer properties against hematological malignancies such as leukemia and lymphoma, and solid tumors, such as breast cancer, thyroid cancer, and osteosarcoma among others (Mohajeri and A.J.C.r.i.o.h. Sahebkar, 2018; Morabito et al., 2004). DOX is a

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widely used and well-established antitumor drug and a key component in many chemotherapy regimens. There is growing evidence that chemotherapy regimens that include DOX are highly effective and superior to those that do not include anthracyclines (Morabito et al., 2004; Singal et al., 2000; Novitzky et al., 2004). DOX, an anthracycline, is isolated from the pigment of fungus *Streptomyces peucetius* var. *Caesius*. Four anthraquinone rings are connected to one amino sugar moiety in its chemical structure (Morabito et al., 2004). In 1950, the antitumor activity of DOX was first revealed, and its application as an antitumor compound was approved in 1963 (Mohajeri and A.J.C.r.i.o.h. Sahebkar, 2018; Morabito et al., 2004). Although other derivatives of DOX were also discovered, DOX has been the most popular antitumor compound due to its high efficacy at low doses (Wallace et al., 2020). The anticancer activity of DOX is attributed to its capacity to interfere with DNA replication and transcription. DOX facilitates multiple roles, including intercalation with DNA, preventing DNA unwinding, and topoisomerase II suppression (Hortobágyi, 1997; Aubel-Sadron and Londos-Gagliardi, 1984; Pang et al., 2013; Tarr and van Helden, 1990; de Jong et al., 1990; Ashrafizadeh et al., 2021a; Mirzaei et al., 2022a). Despite the benefits of DOX in cancer therapy and its ability to impair tumor progression, the application of DOX, especially in clinics, is faced with several challenges and impediments, urging researchers to find solutions. The first difficulty is related to the concentration-dependent toxicity of DOX and its negative impacts on other organs and tissues of the body, especially the heart (Rawat et al., 2021). Another problem is the lack of specific delivery of DOX to tumor tissues, which significantly reduces its potential in cancer suppression. The most significant obstacle with DOX, however, is the development of resistance, such that cancer cells adopt alternate mechanisms to cause chemoresistance. When resistance develops, the susceptibility of cancer cells to DOX falls substantially. Thanks to advances in biology and genetics, the underlying mechanisms and pathways that lead to DOX resistance in cancers can now be understood. Some of the key factors contributing to DOX resistance include abnormal expression of epigenetic factors, gene mutations, increased activity of drug efflux transporters such as P-glycoprotein (P-gp), pro-survival autophagy, and inhibition of apoptosis (Mirzaei et al., 2021a; Yue et al., 2021; Das et al., 2021; Taheri et al., 2022; Taheriazam et al., 2023).

Nanobiotechnology has emerged as a cutting-edge interdisciplinary field for the treatment of diseases in recent years, including cancer and oncology. Nanotechnology has a variety of applications in these fields, including the imaging and diagnosis of cancer through the design of nanoplatforms that can detect cancer biomarkers for early detection (Meng et al., 2016; Peng et al., 2014; Nosrati et al., 2022a; Abbasi et al., 2022). Moreover, nanotechnology has proven to be a promising approach for delivering drugs in cancer therapy. The use of nanoplatforms provides the advantage of targeted delivery of anticancer agents to tumor tissues, resulting in increased internalization (Hashemi et al., 2022; Jan et al., 2022; Salehiabar et al., 2023). Furthermore, because some are stimuli-responsive and targeted, they help to reduce chemoresistance (Ashrafizadeh et al., 2022a). Various anticancer drugs have been delivered by nanostructures as part of a chemotherapeutic regimen, such as docetaxel, paclitaxel, topoisomerase inhibitors, and cisplatin among others, to improve efficacy in cancer therapy (Ashrafizadeh et al., 2022b; Cheng et al., 2021; Chen et al., 2021a; Yang et al., 2021a).

The clinical use of nanoparticles is contingent on their biocompatibility, and lately, there has been a growing emphasis on using environmentally friendly substances like chitosan to modify nanostructures for enhanced biocompatibility. Among the nanostructures that have received approval for drug delivery are lipid-based nanoparticles, which are deemed safe for long-term use (Khan et al., 2022; Cao et al., 2022; Ertas et al., 2021). The purpose of this paper is to examine the function of micellar nanoparticles in the administration of DOX in cancer treatment. We will first provide a description of micelles and their biomedical application and then describe stimuli-responsive micelles such as pH-, redox- and multi-functional micelles for DOX delivery. Next, we explore the potential of micelles to deliver DOX in conjunction with other medications and genetic materials, as well as the impact of surface modification on enhancing the specificity of micelles towards cancerous tissue. The clinical use of micelles and their role in phototherapy are also discussed.

2. Micelles: basics and biomedical applications

Micelles are colloidal dispersions with particle sizes between 5 and 100 nm. Their size depends on the head group type and alkyl chain length (Kabanov et al., 1992; Torchilin, 2007; Schramm and StasiukD.G. J.A.R.S.C. Marangoni, 2003; Kellermann et al., 2004). Aggregation of surfactant molecules in micelles is facilitated by cationic, anionic, zwitterionic, or non-ionic groups (Loppinet and Monteux, 2016). The tail of micelles has a non-polar hydrocarbon chain that can be embedded in the center, forming a ball like structure in aqueous solutions to produce micelles (Chen et al., 2016; Jia et al., 2016). Fatty acids, salts of fatty acid (soap), phospholipids, and similar structures can be utilized for the generation of micelles. When lipids are used in the formation of micelles, nanostructures may have a lower critical micelle concentration (CMC) (Patil et al., 2016). The amphiphilic molecules in aqueous solution undergo self-assembly to generate micelles containing both hydrophilic and hydrophobic sections (Kabanov et al., 1995; Papaioannou et al., 2016; Shah et al., 2016). When the concentration of amphiphiles in a solution decreases, they turn into individual monomers. However, when the concentration is high, self-assembly and clustering takes place, resulting in the formation of micelles (Torchilin, 2007). The formation of micelles is dependent on a certain concentration, referred to as the crucial micelle concentration (CMC). Above the CMC, the dehydration of hydrophobic tails results in the self-assembly and aggregation of amphiphiles into micellar nanoparticles, held together by van der Waals bonds (Torchilin, 2007). In the final structure of a micelle, there is a hydrophilic shell that can connect with the water surrounding micelles via hydrogen bonds (Ferreira et al., 2016). The shape of micelles can vary, including spheres, rods, tubes, vesicles, and sheets, and is dependent on factors such as the type of solvent, length of the blocking chain, temperature, and nature of the blocking agents (Jones and Leroux, 1999; Giorgio et al., 2016; Pottage et al., 2016).

The shape of micelles can vary, including spheres, rods, tubes, vesicles, and sheets, and is dependent on factors such as the kind of solvent, length of the blocking chain, temperature, and nature of the blocking agents. Micelles have gained significant interest in the management of diseases. For example, researchers have produced pH-sensitive micellar nanostructures for oral administration of insulin to treat diabetes mellitus. These nanostructures have a high level of biocompatibility, with insulin being incorporated into their core (Hu et al., 2019). Besides, oral delivery of berberine by micelles has been effective in mediating hypoglycemic levels and improving diabetes mellitus (Kang et al., 2020). In brain disorders such as Alzheimer's disease, micelles have been of interest in reducing oxidative stress and improving glycometabolic activity (Zhang et al., 2022a). Furthermore, multifunctional peptide-assembled micelles have led to a considerable decrease in ROS and amyloid-beta levels in brain disorder treatments (Lei et al., 2021). The function and application of micelles in cancer have been of interest in recent years. Prodrug polymeric micelles can be used to mediate tumor microenvironment remodeling and to integrate cancer-associated fibroblasts in order to inactivate them and improve chemotherapy potential (Zheng et al., 2021). In addition, micelles can be used for imaging cancer and for simultaneous chemotherapy. For the administration of paclitaxel, hypoxia-sensitive micelles have been devised. As well, quantum dots loaded in the core of micelles modified with folic acid can increase their specificity towards tumor cells (Xu et al., 2022). One advantage of using micelles is their ability to deeply penetrate tumors. Loading docetaxel in micelles resulted in the formation of nanoparticles with a particle size of 21.9 nm, which can facilitate a prolonged delivery

of docetaxel using the blood circulation cycle (Yang et al., 2022). Micelles can increase the specificity of drugs to induce apoptosis and ROS to enhance cytotoxicity against tumor cells (Chary et al., 2022). TPGS-loaded triphenyltin micelles can increase the expression level of p53 to stimulate apoptosis in breast tumor cells (Singh et al., 2022). Besides, by combining chemotherapy and phototherapy within micelles, a synergistic cancer treatment can be achieved (Yang et al., 2021b). Surface-modified and stimuli-responsive micelles have enhanced cancer treatment (Cheng et al., 2022). In next sections, we describe the function of micelles in the delivery of DOX.

3. Nanomaterials in delivery of drugs for cancer therapy

Numerous research has utilized nanoparticles for drug delivery, which has proven to be an effective strategy. Before analyzing the function of micelles in DOX distribution, it is preferable to consider the function of nanostructures in drug delivery. The pH- and thermos-sensitive nanostructures can mediate cisplatin delivery and it elevates internalization in tumor cells. Moreover, they mediate controlled release of cisplatin and they suppress tumorigenesis up to 64% (Perera et al., 2022). The cationic lipid nanostructures can be co-loaded with paclitaxel and perfluorohexane, and exposure to irradiation induces release of cargo to cause chemotherapy (Du et al., 2022). The delivery of drugs by nanostructures can increase potential of drugs in tumor suppression and on the other side, it prevents development of drug resistance. It has been reported that co-loading of Rho 123 and MMC on mesoporous silica nanostructures promotes their accumulation and internalization in cancer cells, mediates their sustained release and elevates their cytotoxicity that are beneficial in suppressing multidrug resistance (Igaz et al., 2022). The loading of gemcitabine on polymeric nanostructures results in an increase in cellular uptake of this drug and its modification with EGFRvIII selectively targets ovarian tumor cells (Bhattacharya et al., 2022). Utilizing nanoparticles that have been modified with membranes is one of the recent technologies for cancer treatment delivery. The pH-responsive liposomes have been modified with cancer cell membrane and then, two drugs including RA-V and BMS-202 have been loaded in nanostructures to increase internalization in tumor cells, blood circulation time, apoptosis induction and increasing targeting ability of cancer cells (Yao et al., 2022). More importantly, nanocarriers utilized for delivery of drugs are biocompatible and they can also provide simultaneous imaging of cancer cells (Li et al., 2022a). The crossing over biological barriers can be accelerated by nanostructures and due to increasing local level of drugs at cancer site, nanostructures can suppress drug resistance in cancer (Guo et al., 2022). Moreover, nanoparticles can reduce IC50 of drugs and they increase ability in cell death induction (Patil et al., 2022). Interestingly, co-delivery of chemotherapy drug and siRNA can increase sensitivity of tumor cells and impair progression (Zhang et al., 2022b). Therefore, increasing evidence is line of using nanoparticles for delivery of drugs in potent cancer therapy (Li et al., 2022b; Assali et al., 2022; Pirali-Hamedani et al., 2022). Although it is not related to delivery of DOX, it is noteworthy that nanoparticles may be utilized to remove DOX (Sadrnia et al., 2021) and biosensors to measure its concentration (Alavi-Tabari et al., 2018).

4. Stimuli-responsive micelles

4.1. pH sensitive

The tumor microenvironment is a unique space with differing temperature, pH, and enzyme content. Redox balance is impaired in the tumor microenvironment. Aerobic glycolysis and shifts from oxidative phosphorylation to other metabolism types are reasons for acidic pH levels in tumor microenvironment (Entezari et al., 2023). With the aim of delivering drugs for cancer therapy, nanostructures can be designed to be pH-responsive due to their low pH. This is done by creating acid-sensitive bonds within the nanostructures, making them degradable in the acidic environment of tumors (Zhuo et al., 2020; Kanamala et al., 2016; Yan and Ding, 2020). Nanoscale delivery systems relying on pH use protonation and ionization as their foundation, with ionizable groups being incorporated into the nanoparticle design. When the pH is low and acidic, protonation or charge reversal takes place, leading to changes in the hydrophobic and hydrophilic properties of the nanoparticles, resulting in the release of the cargo. Amino, carboxyl, sulfonate, and imidazolyl groups are among the ionizable groups to consider when designing micelles (Kanamala et al., 2016; Yan and Ding, 2020; Du et al., 2015). This section examines the function of pH-sensitive micelles in DOX transport.

It has been proven *in vitro* and *in vivo* that pH-sensitive micelles increase DOX's anticancer activity. A significant benefit of pH-sensitive micelles is their small size even after incorporating the drug, DOX. In an experiment, pH-sensitive micelles were created using DSPE-PEG2000 and oleic acid and loaded with DOX. The analysis of these nanoparticles showed a low size of 13 nm, a neutral zeta potential, and a high ability to encapsulate the drug. Compared to pH insensitive micelles devoid of any drug, the pH-sensitive DOX-loaded micelles showed greater anticancer activity and fewer side effects than treatment with DOX alone (Cavalcante et al., 2021). The pH sensitivity of micelles depends on the establishment of a bond in structure of micelles that can be degraded upon exposure to low and mild acidic pH of tumor microenvironment. Boronic acid and its derivatives have been used for developing boronic ester bonds that are pH-sensitive by interacting with compounds containing 1,2- or 1,3-diol structures. Therefore, pH-sensitive nanostructures based on boronic acid have been designed for site-specific delivery of drugs to suppress cancer. An example of this process can be seen with the conjugation of mPEG-PCL to CTP to facilitate macro-initiation, followed by the attachment of PDMA to PVBA and to the end of mPEG-PCL. The resulting mPEG-PCL-PDMA and mPEG-PCL-PVBA are then combined to form polymeric micelles in an aqueous solution, and DOX is loaded into these micelles. When this compound is administered to the tumor site, it leads to an accumulation both *in vitro* and *in vivo*, resulting in a significant boost in anticancer activity (Wang et al., 2020). To construct pH-sensitive micelles for the delivery of DOX, the bond between DOX and the micelle must degrade at the acidic condition of the tumor microenvironment. PLL (CB/DOX)-b-PMPC based polymeric micelles are a promising option for delivering DOX in cancer therapy. The poly (L-lysine) block can be utilized to conjugate DOX through imine bonds, and the polymeric micelles can release DOX at the tumor site when exposed to a mildly acidic pH (as shown in Fig. 1) (Ma et al., 2018). One of the important aspects of micelles is their biocompatibility for the delivery of DOX in cancer therapy. It is well documented that polymeric micelles can increase DOX's cytotoxicity against tumor cells via delivery at tumor site and pH responsive drug release. Furthermore, because of the site-specific delivery of DOX, side effects are reduced. The question related to the fate of polymers in the body is also solved, as micelles are biocompatible and can be degraded in the body without causing toxicity (Chen et al., 2021b).

One crucial aspect of improving the delivery of DOX using pH-sensitive micelles is optimizing their sensitivity and specificity through modification. Surface modification of the micelles with ligands has been demonstrated to significantly boost their potential in delivering DOX and improving anticancer activity both *in vitro* and *in vivo*. Several ligands, including folate and peptides, have been used to modify the surface of micelles to enhance their ability for site-specific delivery (Yang et al., 2021c; Zhu et al., 2021a; Guan et al., 2017). Surface modification of micelles is discussed in Section 7. Micelles are comprised of biodegradable polymers and considered promising factors in the delivery of DOX in cancer therapy. Other hydrophobic medications are also capable of being packed into the interior of micelles. Their synthesis is affordable, and their biocompatibility increases the blood circulation duration of anticancer drugs (Biswas et al., 2016; Xin et al., 2016; Chen et al., 2015; Jaskula-Sztul et al., 2016). Besides, micelles can provide

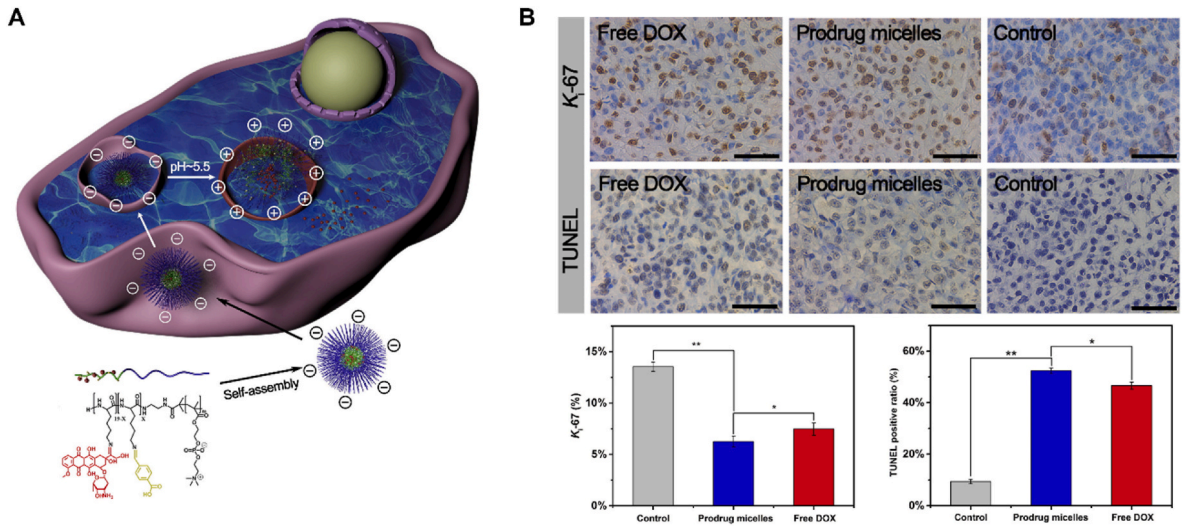

Fig. 1. (A) The self-assembly of DOX-loaded micelles and drug release at low pH level (pH 5.5); (B) Evaluation of apoptosis induction via TUNEL staining. Reprinted with permission from Elsevier (Ma et al., 2018).

enhanced permeability and retention (EPR) to promote the accumulation of drugs at tumor site (Xin et al., 2016; Xu et al., 2015; Yin and Y.H. J.E.j.o.p. Bae, 2009; Bastakoti et al., 2013). In an experiment, dextran-stearic acid (Dex-SA) and dextran-histidine (Dex-His) conjugated polymers were used to synthesize pH-sensitive micelles to deliver DOX at tumor site. Drug release was measured at 76% at an acidic pH, while it was 56% at physiological pH. The nanoparticles effectively increased the uptake of DOX by anticancer agents and suppressed tumor progression (Jafarzadeh-Holagh et al., 2018). Multi-drug resistance (MDR) severely restricts the potential of anticancer therapies (Tóth et al., 2020; Tan et al., 2019; Wu et al., 2014). ATP-binding cassette transporters such as P-glycoprotein (P-gp) are involved in MDR (Schinkel and J.W.J.A.d.d.r. Jonker, 2012; Kathawala et al., 2015; Callaghan et al., 2014; Sosnik, 2013). TPGS is an inhibitor of P-gp and has been approved by the FDA for overcoming MDR via reducing ATP levels and preventing ATPase activity (Zhang et al., 2012a, 2012b; Choudhury et al., 2017). Furthermore, TPGS can mediate ROS generation, apoptosis induction, and DNA damage to reduce cancer viability (Yang et al., 2018a). In a study, star-shaped TPGS copolymers were employed to synthesize pH-sensitive micelles for the delivery of DOX. The application of these TPGS-based micelles in breast cancer therapy resulted in high stability, long-term storage, efficient internalization into cancer cells, and inhibition of multidrug resistance (MDR), as demonstrated in Fig. 2 (Xu et al., 2021). According to these findings, pH-sensitive micelles are viable carriers for site-specific DOX delivery (Guo et al., 2021; Yu et al., 2021; Gao et al., 2019).

4.2. Redox sensitive

Redox species are potential contributing factors in the establishment of stimulus-responsive nanostructures (Li et al., 2020). Tumor cells produce more reactive oxygen species (ROS) than normal cells due to mitochondrial dysfunction (Lee et al., 2013). Glutathione (GSH) is reduced biothiol that is found in living organisms (Estrela et al., 2006), and its levels can reach up to 2–10 mM in cancer cells, 7–10 times greater than normal cells (Zhong et al., 2020). Therefore, both ROS and GSH are important players in tumor microenvironment. Studies have demonstrated that various molecular groups are responsive to GSH and ROS, including disulfide, ditelluride, metal ions, thioketal, and bilirubin, among others, which can be used in developing stimulus-responsive nanocarriers (Yang and Sun, 2022).

Redox-responsive polymeric micelles can be prepared to deliver DOX in cancer therapy and imaging. Polymeric micelles are synthesized from mPEG-ss-Tripp, which are redox-sensitive with a particle size of 105 nm. When GSH is present, the disulfide bonds of micelles are cleaved, releasing DOX at tumor site and suppressing tumor progression in xenografts (Sun et al., 2021). Indomethacin (IND) is considered an anti-inflammatory compound that can suppress MDR and GSH to prevent MRP-mediated chemoresistance (Duffy et al., 1998). IND impairs MRP1 promoter activity and decreases MRP1 expression (Matsunaga et al., 2006). Accordingly, DOX-loaded redox-sensitive micelles have been designed based on dextran and IND with a diameter of 50 nm. There is a disulfide bridge between IND and dextran, which can be degraded by GSH to release drug and suppress breast cancer progression while lowering the development of drug resistance (Zhou et al., 2017). Both hydrophilic and hydrophobic segments are found in amphiphilic block copolymers, which can be used for the development of nanoparticles (Chen et al., 2017; Cheng et al., 2016; Chu et al., 2016). PEG and PLGA are among the most widely used polymers in the development of drug delivery systems. PEG is utilized to enhance internalization and extend blood circulation time, and to prevent opsonization. PLGA, on the other hand, is biodegradable and is efficiently cleared from the body (Chen et al., 2017; Avgoustakis et al., 2003; Zhang et al., 2014). Polymeric micelles based on mPEG-PLGA micelles have been used to deliver DOX in cancer therapy. These micelles are redox-responsive with a particle size of 123.9 nm. The encapsulation efficiency of micelles was found to be 54.9%, and when exposed to GSH, it resulted in the release of 73.94% of DOX. These nanostructures enhanced the accumulation of DOX in tumor cells and increased cervical cancer suppression (Fig. 3) (Birhan et al., 2019).

It has been reported that pro-inflammatory cytokines and growth factors play crucial role in cancer metastasis (KozłowskiandKozłowskaJ.J.P.H.i.M.D. Kocki, 2015; Su et al., 2015). For instance, overexpression of cyclooxygenase-2 (COX-2) increases the viability and proliferation of tumor cells (Güler et al., 2016; Sun et al., 2017). Besides, inflammatory factors can facilitate angiogenesis induction and promote cancer metastasis (Regulski et al., 2016; Yu et al., 2016). As such, anti-inflammatory factors, including ibuprofen, have been utilized to suppress cancer progression (Said-Elbahr et al., 2016). An effort was made to develop redox-responsive hyaluronic acid-ibuprofen prodrug micelles for the administration of DOX to inhibit breast cancer metastasis. The use of ibuprofen was based on its ability to downregulate COX-2 and suppress metastasis. The ibuprofen was conjugated to hyaluronic acid through disulfide bonds, which then self-assembled for the delivery of DOX. Upon redox stimulation, the ibuprofen was released and, in conjunction with hyaluronic acid, delivered DOX to inhibit

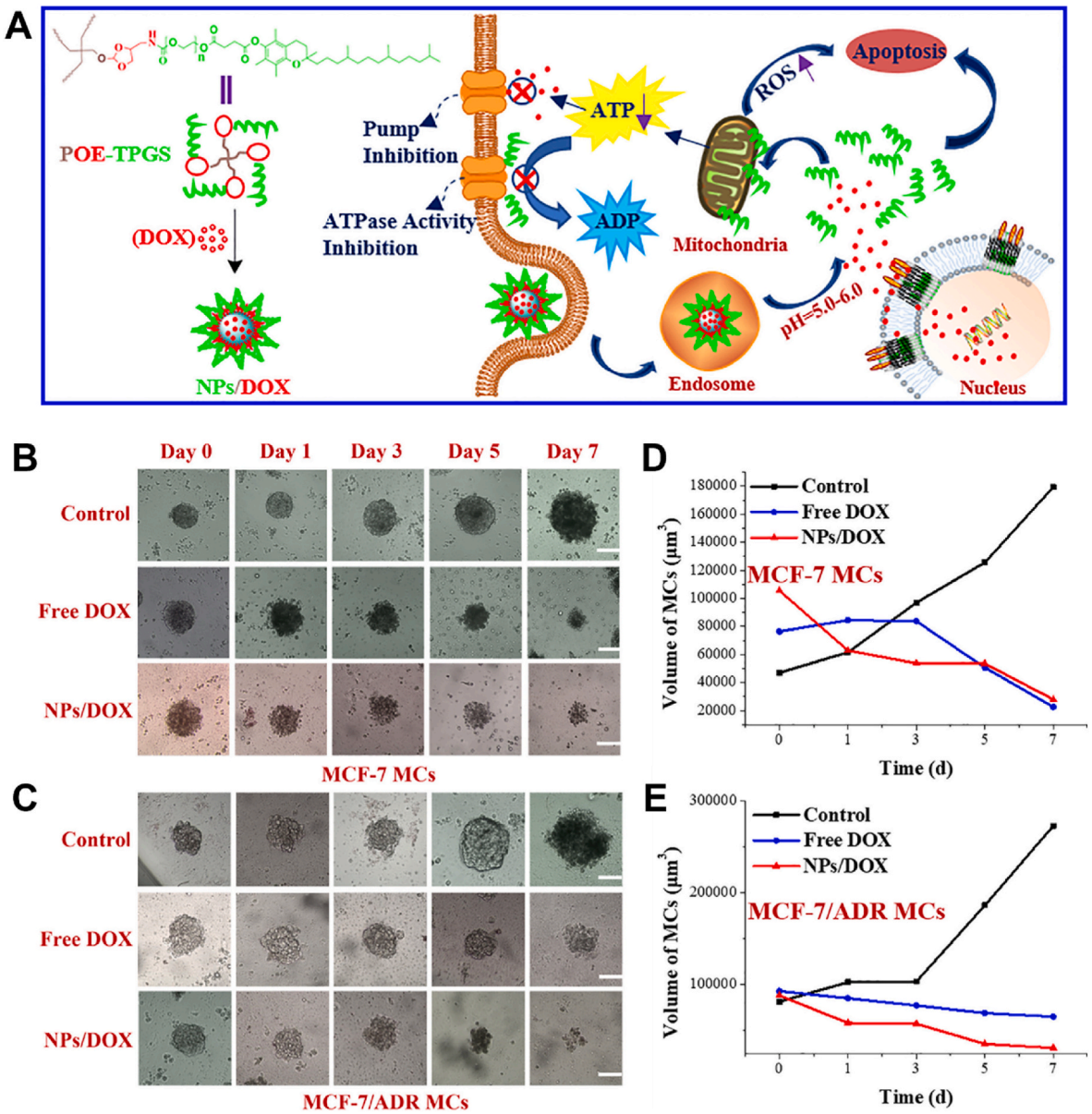

Fig. 2. (A) The preparation of micelles and their ability in apoptosis induction in tumor cells; (B–E) Suppressing growth of breast tumor cells. Reprinted with permission from Elsevier (Xu et al., 2021).

breast cancer invasion (Chai et al., 2020). In addition, redox-responsive micelles have been used for the co-delivery of DOX and paclitaxel (Yang et al., 2019). Paclitaxel prevents depolymerization of microtubules to suppress cancer (Ashrafizadeh et al., 2021b; Mahabady et al., 2022). Furthermore, DOX also impairs topoisomerase activity for tumor suppression. The combination of DOX and paclitaxel, as well as their co-delivery by redox-responsive micelles, has been shown to have synergistic effects on tumor suppression. Even with the double dose of drugs, the particle size of nanostructures remains small (98.5 nm) (Yang et al., 2019). Heparosan (HEP), a linear polysaccharide with potential use in biological pharmacy, has garnered more attention in recent years (DeAngelis Paul, 2013). HEP has structural similarities to heparin and heparan sulfate and is isolated from fermentation broth, which reduces the risk of contamination (Xu et al., 2011; Wu et al., 2015; Zhang et al., 2012c). In an experiment, HEP and deoxycholic acid conjugates (HSDs) were used for developing stable micelles with 100% DOX release at a 10 mM concentration of GSH. These nanostructures are biocompatible and can suppress tumor progression by enhancing DOX's cytotoxicity, which is internalized through clathrin-mediated endocytosis in laryngopharyngeal tumor cells (Fig. 4) (Sun et al., 2018).

4.3. Light responsive

Treatment of osteosarcoma with DOX, a popular chemotherapy agent, has generated considerable interest. The efficacy of DOX in suppressing osteosarcoma is not only low, but the development of resistance to DOX is also high (Guan et al., 2021; Li et al., 2021). In an experiment, light-responsive polymeric micelles for DOX delivery were created by coating them with PEG to avoid protein absorption and the formation of a protein corona on the nanoparticle surface. When exposed to ultraviolet radiation, the bond between DOX and PEG (amide bond) is disrupted, allowing for the release of DOX from the micelles to inhibit the progression of osteosarcoma (Chen et al., 2021c). Recently, there has been a shift in focus towards the development of light-responsive nanostructures utilizing 2-nitrobenzyl-containing UV-sensitive polymers and UCNPs, to achieve a high level of control over drug release (Liu et al., 2017a). Exposure to ultraviolet light leads to a photochemical reaction in 2-nitrobenzyl derivatives that disrupts

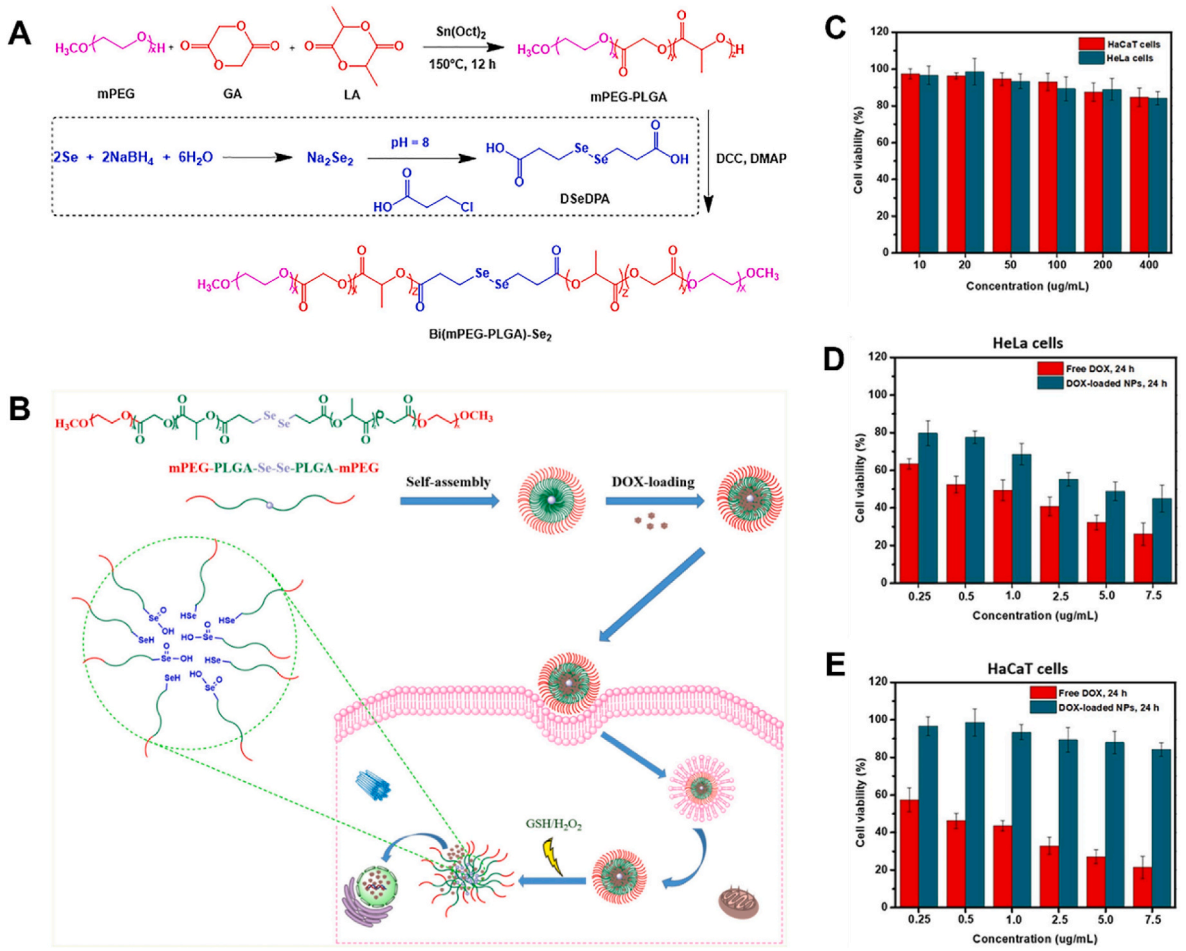

Fig. 3. (A–B) Synthesis method of micelles, DOX loading and internalization in tumor cells; (C–E) The cytotoxicity of DOX-loaded micelles against tumor cells. Reprinted with permission from Elsevier (Birhan et al., 2019).

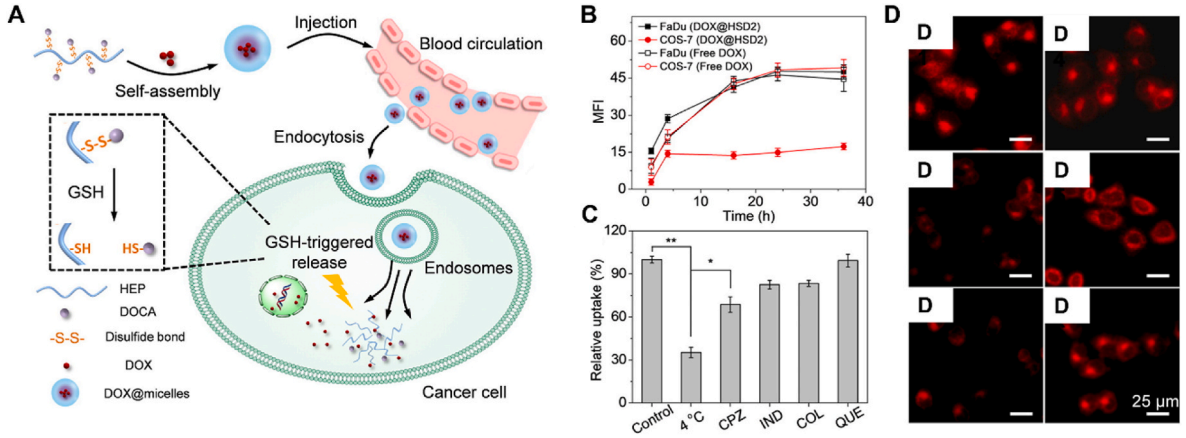

Fig. 4. (A) DOX loading in GSH-responsive micelles and endocytosis uptake by tumor cells; (B–D) DOX-loaded GSH-responsive micelles in internalization in tumor cells. Reprinted with permission from Elsevier (Sun et al., 2018).

hydrophilic-hydrophobic balance and cleaves photocaged linkages for drug delivery (Wang et al., 2014). Besides, conversion of NIR light to ultraviolet/visible light can be facilitated by UCNPs to mediate photochemical reactions and remote regulation (Yao et al., 2016). As part of the effort to improve drug delivery and bioimaging, NIR-light-activated hybrid micelles were developed for DOX delivery. These nanoarchitectures are comprised of UCNPs, DOX, and ultraviolet-light-responsive amphiphilic block copolymers, allowing for both imaging and chemotherapy. Upon exposure to NIR radiation, the UCNPs convert the NIR light into ultraviolet light, triggering a photoreaction process that releases DOX. This release of DOX is crucial for both imaging and the degradation of the micelles to combat cancer (Fig. 5) (Chen et al., 2020).

Light-responsive micelles are used for co-delivery of DOX with other agents. Polymeric micelles are synthesized from 3-hydroxyflavone (3-HF) derivatives and an ether linker. The photo-responsive feature of

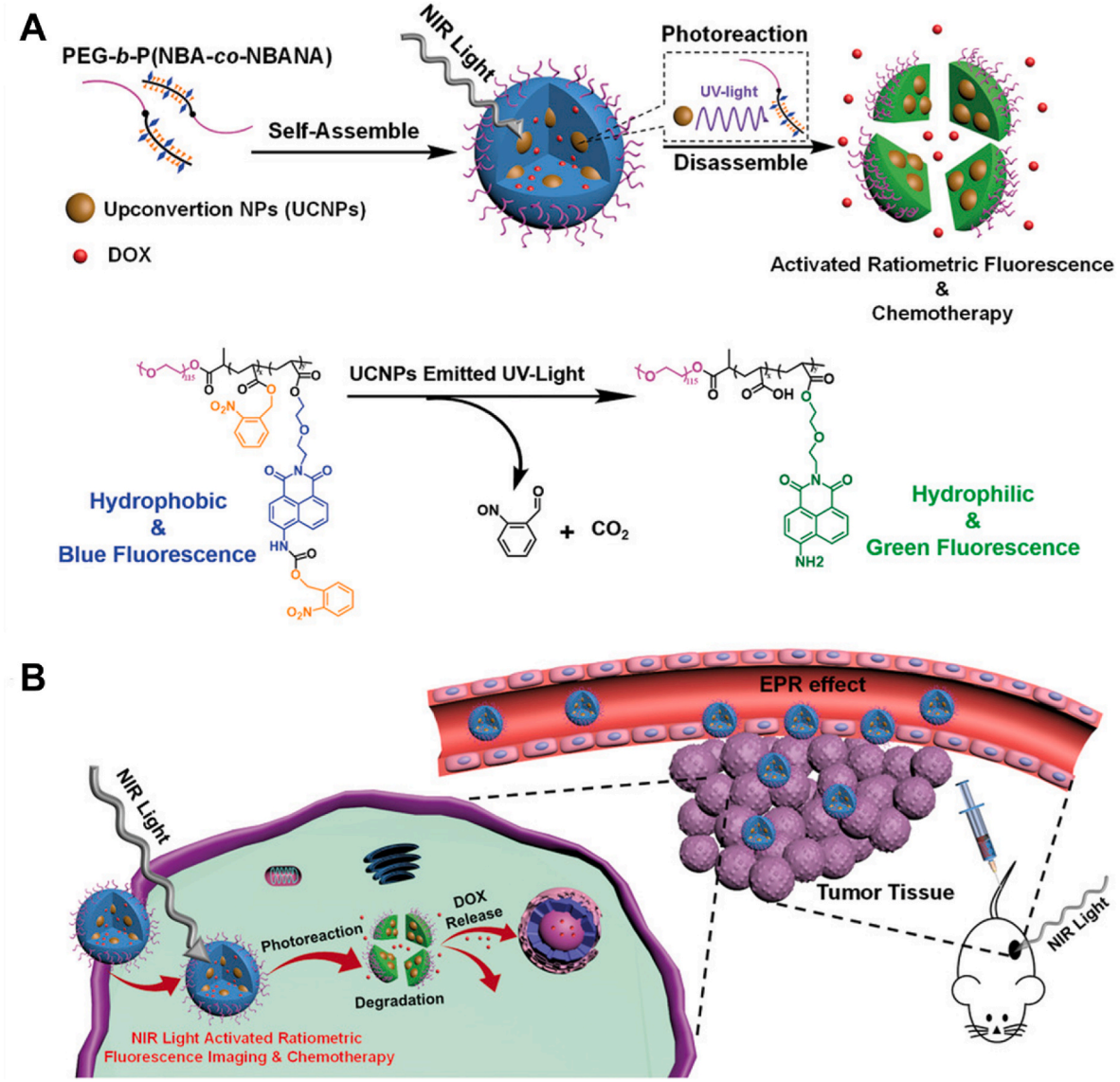

Fig. 5. (A and B) Preparation of photoreactive-DOX-loaded micelles for cancer therapy and ability of DOX release after irradiation in cancer therapy. Reprinted with permission from Wiley (Chen et al., 2020).

polymeric micelles results from the nitrobenzyl ether group and 3-HF derivatives, which are used for carbon monoxide and formaldehyde release. Furthermore, photo-responsive polymeric micelles are promising for the delivery of DOX and providing a sustained release to suppress tumor progression (Zheng et al., 2022). Diels-Alder (DA) click reaction is one of the methods that can be used for the synthesis of polymeric micelles and for developing light-responsive nanocarriers (Rammal et al., 2021). Initially, indocyanine green (ICG) is loaded, and then DOX is loaded into polymeric micelles through a crosslinking reaction. Upon exposure to NIR light, DOX is released, leading to the impairment of cancer cell survival (Yadav et al., 2021). Therefore, light-responsive nanocarriers are ideal candidates for DOX delivery because they provide much better control over drug release when compared to other nanoparticles that are not sensitive to endogenous stimuli.

4.4. Multifunctional

Efforts have been made to create multifunctional nanocarriers based on micelles for efficient delivery of DOX. Light- and pH-sensitive micelles were created using PEG-b-PEDNB-b-PEG through sequential thiol-acrylate Michael addition polymerization. The o-nitrobenzyl linkages in these micelles are light-cleavable, while the acid-labile β-thiopropionate linkages are present in the structure of PEG-b-PEDNB-b-PEG. This triblock copolymer can self-assemble into micellar nanoparticles, making it suitable for DOX delivery. With both o-nitrobenzyl and β-thiopropionate linkages, these micelles can degrade in response to light and pH, releasing DOX for the suppression of lung cancer (Jin et al., 2014). Previous studies have shown that DOX-loaded micelles can be designed to respond to both internal and external stimuli. In one experiment, pH- and GSH-sensitive micelles were created by conjugating them with HA and MP. The anti-CD44 antibody prevented the internalization of these nanoparticles in cancer cells, indicating that HA modification is crucial for the accumulation of micelles. These pH- and GSH-sensitive micelles release DOX at the tumor site, leading to cell cycle arrest. Furthermore, DOX-loaded micelles effectively eliminate cancer stem cells in colon cancer (Fig. 6) (Debele et al., 2018).

In cancer treatment, multifunctional micelles have been found to be beneficial in providing both chemotherapy and immunotherapy. An experiment created chitosan-coated HA micelles for the delivery of DOX and siRNA-PD-L1 in a combination of chemotherapy and immunotherapy. These biocompatible micelles had a particle size of 180 nm. The

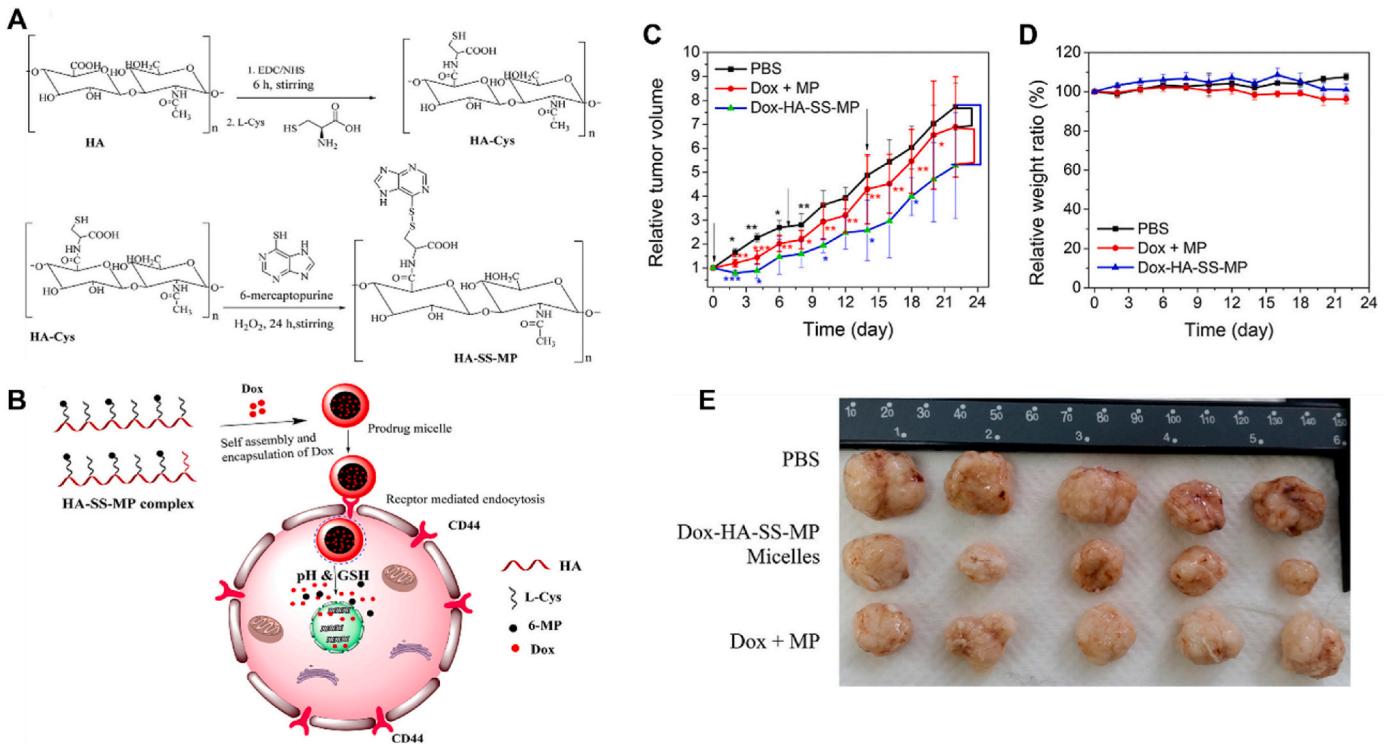

Fig. 6. (A and B) Synthesis method of micelles and their mechanism of action in cells; s (C–E) The efficacy of DOX-loaded micelles *in vivo* in tumor suppression. Reprinted with permission from ACS (Debele et al., 2018).

HA modification enabled the uptake of micelles in breast tumor cells through binding with the CD44 receptor. By silencing PD-L1, these micelles enhanced the infiltration of CD4+/CD8+ T cells in the tumor microenvironment. The release of the cargo from these micelles was pH- and redox-sensitive, which facilitated the site-specific delivery of DOX and siRNA (Song et al., 2022). The role of stimuli-responsive micelles in DOX delivery and cancer suppression is demonstrated in Table 1.

5. Micelles in doxorubicin and drug combination delivery

Efforts have been made to increase the efficacy of DOX in the treatment of cancer by combining it with other anticancer drugs to combat DOX resistance and boost tumor suppression. Nevertheless, adequate delivery of both drugs to the tumor site is essential. In order to do this, nano-scale delivery methods, such as micelles, have been designed for the co-delivery of DOX and anticancer drugs. An amphiphilic triblock copolymer was created through a two-step ring-opening

Table 1
The role of stimuli-responsive micelles in DOX delivery.

Nonvehicle	Stimulus	Cancer type	Remark	Ref
Dextran-based micelles	Redox-responsive	Breast cancer	DOX release in a reducing environment Suppressing tumor progression *in vitro* and *in vivo* High stability in physiological environment and drug release at tumor microenvironment	Zhou et al. (2017)
Prodrug micelles	pH-responsive	Breast and cervical cancers	Preparation of micelles from 4-carboxy benzaldehyde-grafted poly (L-lysine)-*block*-poly (methacryloyloxyethyl phosphorylcholine) (PLL (CB/DOX)-b-PMPC) copolymer Drug release at tumor pH level High suppression of cancer cells	Ma et al. (2018)
Prodrug micelles	pH-responsive	Breast and lung cancers	Co-delivery of DOX and paclitaxel for synergistic cancer therapy 110.5 nm particle size Drug release at low pH levels	Jiang et al. (2020)
Polymeric micelles	pH-responsive	Breast cancer	Preparation of micelles from DSPE-PEG2000, oleic acid, and DOX Dimeter of 13 nm Zeta potential near to neutrality Suppressing tumor growth	Cavalcante et al. (2021)
PEGylated nanoparticles	Reduction-responsive	Breast cancer	Intracellular accumulation and release of drug upon reaching to cancer site Reduction-sensitive release of cargo and inhibiting tumorigenesis	Wang et al. (2021a)
Dextran-Stearic Acid (Dex-SA) and Dextran-Histidine (Dex-His) conjugated polymeric micelles	pH-sensitive	Glioblastoma	Drug release at low pH level, increased cellular uptake and anti-proliferative activity	Jafarzadeh-Holagh et al. (2018)
Targeted poly-peptide nanomicelles	pH-responsive	Breast cancer	Particle size of 121.64 nm Release of 73.52% of drug at 24 h in pH 4.5 Apoapsis induction Reducing cancer proliferation	Zhu et al. (2021a)

polymerization followed by hydrophobic interactions, which allowed for DOX encapsulation by micelles. Then, cisplatin was loaded into the micelles via Pt-carboxyl coordination interactions, which boosts the micelles' stability and inhibits DOX release at physiological pH. Upon internalization in the endosome/lysosome, the low pH environment weakens the Pt-carboxyl coordination interactions, leading to the release of DOX and cisplatin from the micelles and tumor suppression (Gao et al., 2020). The anticancer activity of cisplatin is based on the generation of adducts with DNA that led to DNA damage and apoptotic cell death. However, the potential of cisplatin in cancer chemotherapy has decreased due to development of resistance (Mirzaei et al., 2021b). Therefore, the DOX and cisplatin combination has the potential to successfully battle cancer. Redox-sensitive micelles have been designed for the delivery of DOX and cisplatin in cancer therapy. The process involves conjugating DOX to carboxymethyl chitosan, which then self-assembles into micelles with a particle size of 274 nm. The release of the cargo from these micelles was shown to be responsive to GSH, leading to the uptake of DOX and cisplatin and hindering tumor growth (Zhang et al., 2017). Similar to cisplatin, docetaxel is also widely utilized in cancer therapy, and its mechanism of action is based on preventing the depolymerization of microtubules and mediating cell cycle arrest (Ashrafizadeh et al., 2021b). The combination of DOX and docetaxel and their delivery through micelles is crucial in cancer treatment. Micelles made of poly (lactic acid), poly (ethylene glycol), and folate (PLA--PEG-FOL) have been developed to carry both docetaxel and DOX. The addition of folate to the micelles enhances their targeting to tumor cells. The synergistic effects of these drugs have proven to be a valuable contribution to cancer therapy (Hami et al., 2017). Micelles composed of mPEG-PCL were conjugated with both DOX and docetaxel using redox-responsive disulfide bonds. The resulting particles, with a size of 223.7 nm, were formed by mixing DOX- and docetaxel-loaded micellar nanoparticles. These micelles exhibit high cellular uptake in MCF-7 cells, effectively suppress tumor progression, and demonstrate synergistic effects through the co-delivery of both docetaxel and DOX (Fig. 7) (Wu et al., 2018).

Micelle-mediated co-delivery of DOX and chemotherapeutic drugs is effective in suppressing cancer (Jiang et al., 2020; Huang et al., 2016; Duong and Yung, 2013; Leonhard et al., 2015). More importantly, natural products have been used to increase the efficacy of chemotherapeutic agents in cancer treatment (Chavda et al., 2021). Since natural products have poor bioavailability, nanoscale delivery systems can be developed to aid with their delivery (Ahmadi et al., 2019). Micelles are potential alternatives for natural product delivery with DOX in cancer treatment. Derived from *Curcuma longa*, curcumin, is effective in cancer therapy because it can induce apoptosis, reduce the expression of oncogenic factors, and prevent tumor metastasis (Ashrafizadeh et al., 2020a, 2020b, 2020c). Poly (ethylene glycol)-block-poly (lactide) (PEG (2 k)-PLA(5 k) amphiphilic copolymeric micelles are synthesized and then loaded with DOX and curcumin. This combination showed superior activity in preventing the growth of breast tumor cells compared to DOX and curcumin alone. Drug-loaded micelles reduced the efflux of DOX in breast tumor cells by downregulating P-gp and suppressing ATP activity to reverse drug resistance (Lv et al., 2016). Resveratrol is another natural product of interest due to its cardioprotective features (Gran et al., 2021; Wang et al., 2022a). Resveratrol can be isolated from natural sources, including grapes, peanuts, and blueberries, in a biologically active form known as *trans*-resveratrol (Gran et al., 2021; Mirzaei et al., 2022b). Recently, delineating the role of resveratrol in cancer therapy and drug sensitivity has been a key focus (Mirzaei et al., 2022b). Polymeric micelles were created using PEG-*b*-PCL and EG-*b*-PBCL and used to deliver resveratrol and DOX. The encapsulation efficiency was reported to be 87.7%, and the combination with resveratrol resulted in more inhibitory impacts on the proliferation of cervical cancer cells compared to DOX or resveratrol alone (Table 2) (Washington et al., 2018).

6. Micelles in doxorubicin and gene co-delivery

Owing to its complexity, the treatment of cancer requires interdisciplinary approaches, and gene therapy has emerged as an option. Although gene therapy was launched as a contemporary and unique treatment for cancer, its effectiveness is limited. The development of drug resistance threatens the efficacy of chemotherapy. Resistance is developed in part due to the degradation of delivered genes by enzymes, the low circulation time, and the low internalization of tumor cells due to their having similar charges as the cell membrane. Nanocarrier research has accelerated in order to overcome these obstacles. Recently, delivery of genetic tools by nanostructures has been a promising strategy in cancer treatment and reversing drug resistance (Ashrafizadeh et al., 2020d, 2021c; Mirzaei et al., 2021c). More importantly, doxorubicin co-delivery with genetic tools has been investigated (Ashrafizadeh et al., 2022c), but more research is needed to pave the way for clinical application and treatment in cancer patients. The current section focuses on the co-delivery of DOX with genes by nanostructures for cancer therapy. RNA interference (RNAi) has been introduced as an effective strategy in the treatment of viral infections and cancer (Dykxhoorn and NovinaP.A.J.N.r.M.c.b. Sharp, 2003; Li et al., 2005). However, an appropriate delivery is vital for RNAi (Zimmermann et al., 2006).

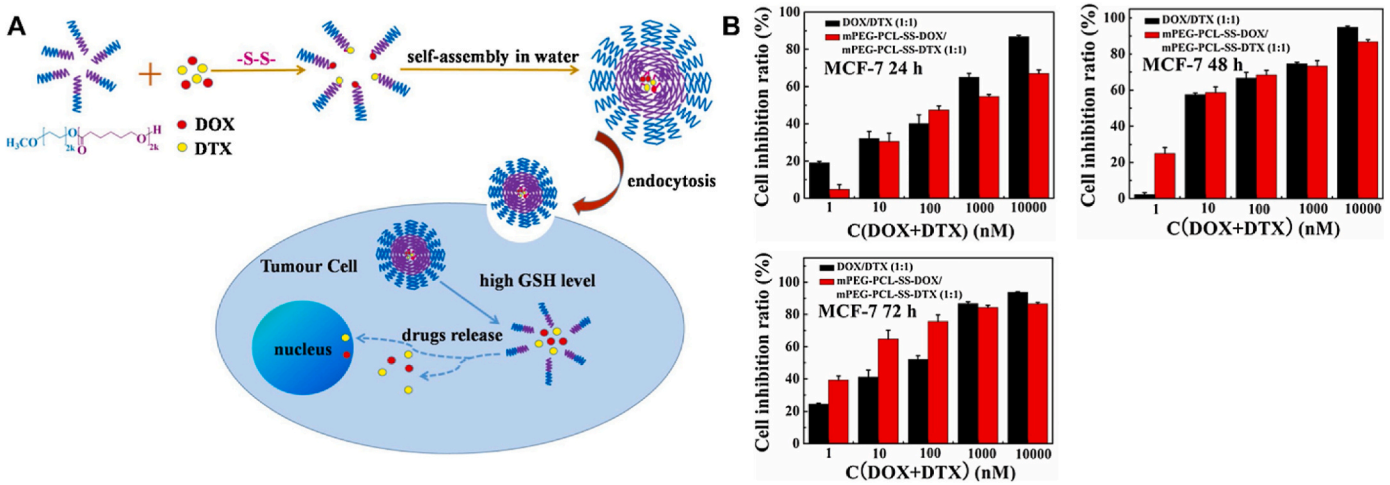

Fig. 7. (A) Co-delivery of DOX and DTX by micelles and internalization in tumor cells via endocytosis in cancer inhibition; (B) Viability of breast tumor cells after exposure to drug-loaded micelles. Reprinted with permission from Elsevier (Wu et al., 2018).

Table 2
The role of micelles in co-delivery of DOX with anticancer agents.

Nanovehicle	Cancer type	Drugs	Remarks	Refs
Polymeric micelles	Breast cancer	thioridazine and doxorubicin	Suppressing tumor growth in a synergistic way Reducing number of cancer stem cells	Ke et al. (2014)
Poly (lactic acid)-poly (ethylene glycol)-folate-based polymeric micelles	Ovarian cancer	Docetaxel and doxorubicin	Particle size of 185 nm and drug release in a pH-sensitive manner High cellular uptake Enhanced cytotoxicity	Hami et al. (2017)
pH-responsive β-cyclodextrin grafted micelles	Breast cancer	Doxorubicin and conferone	34.5 nm particle size Apoptosis induction through intrinsic pathway	Rahmani et al. (2021)
Thermoresponsive Polymeric Micelles	Hepatocellular carcinoma	Doxorubicin and Quercetin	Biodegradable and biocompatible nanocarriers Synergistic cancer therapy	Soltantabar et al. (2020)
Soluplus®-TPGS mixed micelles	Breast cancer	Dihydroartemisinin and doxorubicin	Encapsulation efficiency of 90% Reduced systemic toxicity Increased cytotoxicity against tumor cells	Wang et al. (2019)
Amphiphilic Copolymeric Micelles	Breast cancer	Doxorubicin and Curcumin	Suppressing proliferation Decreasing ATP levels P-gp down-regulation Revering chemoresistance	Lv et al. (2016)
hyaluronic acid-vitamin E succinate (HA-VES) graft copolymer-based micelles	Breast cancer	Doxorubicin and curcumin	High colloidal stability Apoptosis induction Enhanced cellular uptake	Ma et al. (2017)
Anti-GLUT1 antibody-targeted polymeric micelles	Colon cancer	Curcumin and doxorubicin	High tumor suppression and enhanced survival of animal models	Abouzeid et al. (2013)
Multi-functional micelles	Human carcinoma KB cell line	Doxorubicin and paclitaxel	Prolonged drug release Increased penetration Synergistic impact	Duong and Yung (2013)

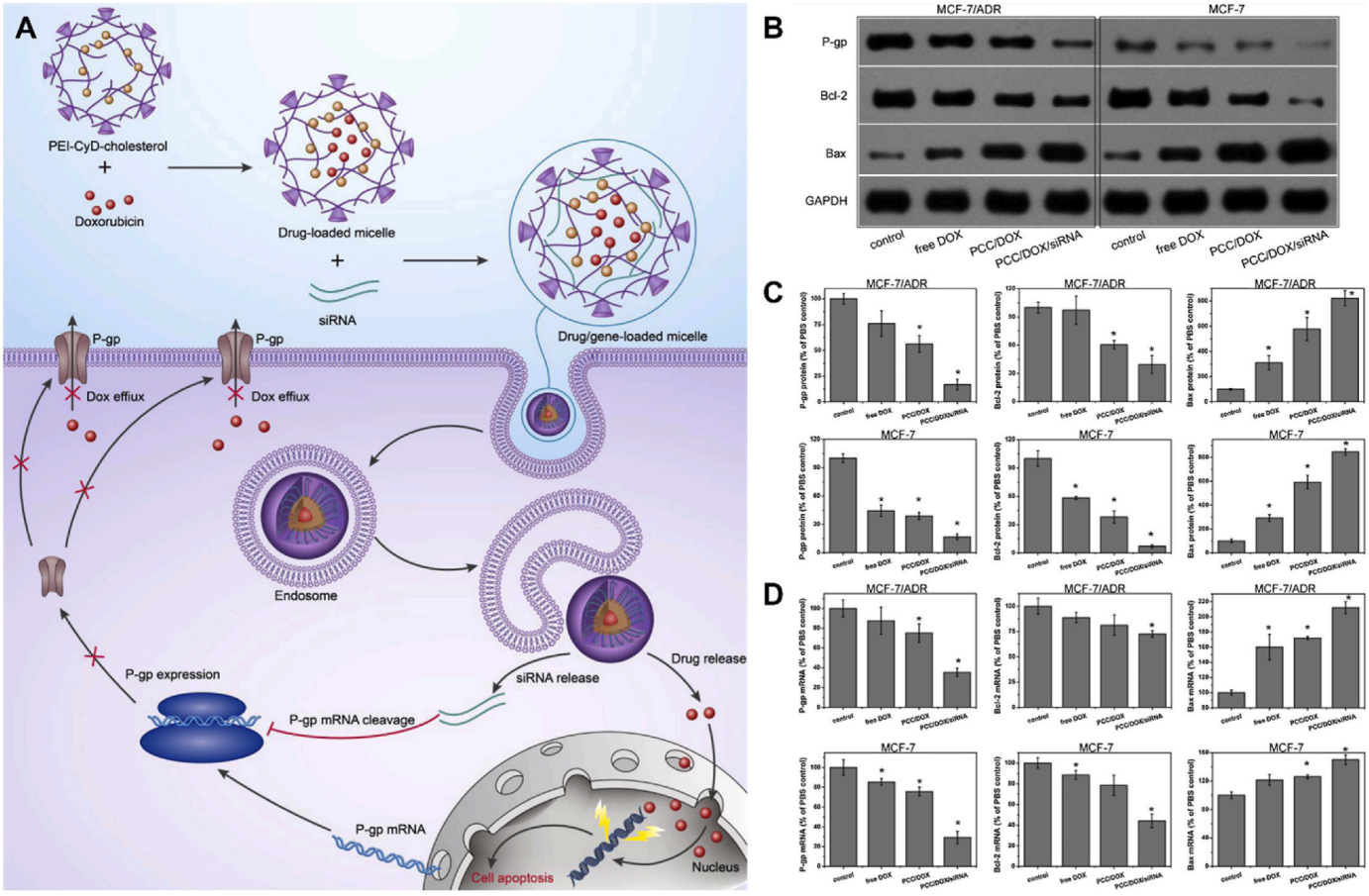

Fig. 8. (A) DOX-loaded micelles for increased cellular uptake and inhibition of P-gp to prevent efflux of DOX from tumor cells; (B) expression level of P-gp and apoptosis-related protein using Western blot; (C and D) Analysis of results obtained from Western blot. Reprinted with permission from Elsevier (Shen et al., 2014).

Cationic polymers and lipid-based nanoscale delivery systems are now appropriate non-viral vectors for cancer therapy and delivery of small interfering RNA (siRNA) (Akinc et al., 2008). In this regard, an experiment has developed cholic acid-polyethylenimine micelles for the delivery of siRNA and DOX for colorectal cancer therapy. The 150 nm particle size, +12 mV zeta potential, and 61.2% entrapment efficiency of drug- and gene-co-loaded micelles are significant advantages. Micelles can also be modified with folate. This nanoformulation stimulates apoptosis and necrosis in colorectal cancer cells, and modification with folate increases anticancer activity (Amjad et al., 2015). One of the most promising approaches to increasing drug sensitivity is preventing the activity of drug efflux transporters. In cancers, an upregulation of P-gp, MRP, and BCRP transporters is observed (Gottesman and FojoS.E.J.N.r. c. Bates, 2002). These transporters have a high substrate specificity and increase xenobiotics efflux (Lage and sciences, 2008). P-gp is encoded by MDR-1 and decreases the accumulation of chemotherapy agents in tumor cells (Hilgendorf et al., 2007; Szakács et al., 2004). A mixed dendrimer micelle has been synthesized for the delivery of siRNA-MDR1 and DOX for cancer therapy. Modification of these nanoparticles with the monoclonal antibody 2C5 can aid better identify tumor cells via cell-surface-bound nucleosomes. Subsequently, internalization of nanoparticles in tumor cells increases to suppress tumor progression and spheroid formation via the release of siRNA and DOX (Pan et al., 2020).

Due to the significance of P-gp in the development of MDR, there has been interest in the use of P-gp-siRNA to enhance DOX sensitivity. Micelles are widely exploited in cancer treatment for the transport of medicines and nucleic acids (Shapira et al., 2011; Dai et al., 2011; Chen et al., 2014a; Xiong and Lavasanifar, 2011). They are a suitable delivery mechanism for siRNA with chemotherapy as they can mediate the release of siRNA sooner than chemotherapy agents. Therefore, activity of drug efflux pump is suppressed, and sensitivity to chemotherapy agent is enhanced (Duan et al., 2013). In an experiment, self-assembled micelles were developed from PEI-CyD loaded with DOX in the core of nanostructures. Besides, siRNA can be conjugated to outer PEI-CyD via electrostatic interaction for optimal cellular delivery of siRNA and DOX to increase the sensitivity of tumor cells to chemotherapy (Fig. 8) (Shen et al., 2014).

The use of stimuli-responsive micelles in DOX delivery has been demonstrated in previous sections. These nanocarriers are designed for the co-delivery of drugs and genes for cancer therapy. Specifically, pH- and redox-sensitive micelles are designed for the co-delivery of DOX and PLK-1-siRNA for cancer suppression. Low molecular weight poly (styrene-*alt*-maleic anhydride) is utilized for the synthesis of smooth, spherical polymeric micelles. Then, DOX and PLK-1-sIRNA are loaded onto micelles, and nanostructures are coated with bovine serum albumin (BSA) to increase their stability. The release of DOX and siRNA occurs in the presence of 10 mM GSH and low pH (5), which suppress tumor progression synergistically (Aji Alex et al., 2017). Therefore, it is highly suggested to deliver siRNA along with DOX for cancer suppression. Similar to siRNA, shRNA can also be applied to decrease the expression level of tumor-promoting genes. Intriguingly, co-delivery of DOX with shRNA by nanoparticles overcomes DOX's insensitivity. PLK-1 exerts an oncogenic function, and its inhibition by miR-23a or nanostructures can impair tumorigenesis (Kollur et al., 2021; Chen et al., 2018). pH- and redox-sensitive micelles have been developed for the delivery of DOX and PLK-1-shRNA for glioma suppression. In the structure of polymeric micelles, there are repeating units containing disulfide bonds. After internalization in cancer cells, the "proton sponge effect" causes lysosomal escape and delivers shRNA and DOX to suppress glioma progression (Wang et al., 2018). Nevertheless, there are limitations in the use of micelles for the co-delivery of DOX and shRNA in cancer therapy. Furthermore, CRISPR/Cas9 system delivery with DOX might be explored as a potent genetic weapon for cancer treatment. Table 3 summarizes the use of gene and drug co-loaded micelles for cancer therapy.

7. Micelles, doxorubicin delivery and phototherapy

When the temperature of the tumor microenvironment rises over 42 °C, cancer cell elimination can occur (Wei et al., 2022; Ashrafizadeh et al., 2022d). Photothermal therapy (PTT) is a new emerging therapeutic tool for cancer cell ablation and is based on transforming light energy into heat at tumor site mediated by photothermal compounds. Based on the tolerance variance between normal and cancer cells, PTT can specifically kill tumor cells with only partial side effects on normal cells. Therefore, after the localization of photothermal agents at a certain site, irradiation can be performed. However, there should be nanoscale delivery systems for specific delivery of these photothermal agents at tumor site (Lv et al., 2021). The significance of PTT in increasing the temperature of the tumor's microenvironment, cancer cell elimination, and chemotherapy effectiveness is becoming more evident (Wang et al., 2021b, 2022b; Chen et al., 2021d, 2021e, 2021f). Similarly, photodynamic therapy (PDT) is utilized in cancer therapy to enhance reactive oxygen species (ROS) production and mediate tumor cell death (Ji et al., 2022a). In recent years, nanoparticle-mediated photodynamic therapy (PDT) has been a hot subject, not only for inhibiting tumor development but also for boosting cancer cell sensitivity to chemotherapy (Dhilip Kumar and Abrahamse, 2021; Zhu et al., 2021b). The aim of the current section is to evaluate the contribution of micellar-loaded DOX nanoparticles to the enhancement of phototherapeutic tumor ablation.

Table 3
Drug and gene co-loaded micelles for cancer therapy.

Nanoparticle	Drug and gene	Cancer type	Remark	Ref
Folate-conjugated cholic acid-polyethyleneimine micelles	Doxorubicin VEGF-siRNA	Colorectal cancer	CO-delivery of siRNA and DOX in VEGF down-regulation and increasing drug sensitivity	Amjad et al. (2015)
Monoclonal antibody 2C5-modified mixed dendrimer micelles	Doxorubicin MDR-1-siRNA	Ovarian cancer	Recognition of tumor cells due to surface modification Preventing drug resistance	Pan et al. (2020)
BSA-stabilized micelles	Doxorubicin PLK-1-siRNA	Breast cancer	Enhanced stability of micelles due to modification with BSA Release of drug in response to GSH and low pH levels High anticancer activity *in vitro* and *in vivo*	Aji Alex et al. (2017)
Graft copolymeric micelles	Doxorubicin PLK-1-siRNA	Breast cancer	Penetrating into endolysosomal membrane Complexation of siRNA with arginine-lysine conjugates Co-localization in cytoplasm of nanoparticles	Aji Alex et al. (2016)
Polymeric micelles	Doxorubicin MDR-1-siRNA	Breast cancer	Co-delivery of drug and gene, and modification with peptide increases tumor selectivity	Xiong et al. (2010)
Polypeptide cationic micelles	ZEB1-siRNA Doxorubicin	Lung cancer	Down-regulation of ZEB1 to suppress EMT and increased DOX sensitivity	Fang et al. (2014)
pH- and redox-sensitive micelles	PLK-1-shRNA Doxorubicin	Glioma	Release of cargo in response to GSH and low pH levels to increase tumor suppression	Wang et al. (2018)

7.1. Photothermal therapy

The development of phototherapeutic agents using polymeric micelles has been critical in increasing the cytotoxicity of DOX against cancer cells. Light-absorbing compounds with phototherapy activity are incorporated into the micelle structure. In a study, poly (dithienyldiketopyrrolopyrrole) (PDPP) polymers were used to create polymeric micelles loaded with DOX. PDPP can absorb near-infrared light at a wavelength of 700–1000 nm and produce heat, serving as a photothermal agent. The micelles showed high stability even after exposure to 808-nm laser radiation. The DOX loading has some influence on the micelle particle size and photothermal potential. The F127 polymer with thermosensitive properties caused the swelling of the micelles for the release of DOX, providing both photothermal therapy and chemotherapy (Liu et al., 2017b). Interestingly, micelles can also be loaded with light-absorbing dyes for PTT and cancer imaging. In a study, micelles were made from dextran-polylactide (DEX-PLA) copolymers and loaded with both DOX as an anticancer agent and DiR as a near-infrared dye. The micelles showed good physical activity and favorable photothermal stability. They were able to accumulate at tumor sites, providing both chemotherapy and PTT for image-guided cancer treatment (Shi et al., 2021). Poly [2,6-(4,4-bis-(2-ethylhexyl)-4*H*-cyclopenta [2,1-*b*;3,4-*b*′]dithiophene)-*alt*-4,7 (2,1,3-benzothiadiazole)] (PCPDTBT) is a polymer containing both an aromatic ring and a heterocyclic ring with photoacoustic activities. These components make them absorb light at a wavelength of 650–900 nm (Arca et al., 2013; Baeg et al., 2013). PCPDTBT, specifically, enables the conversion of light to heat in order to induce necrosis in tumor cells (Li et al., 2016; Zhang et al., 2016). GSH-sensitive micelles consisting of DOX and semiconducting polymer dots are gaining popularity as a cancer therapy solution. These micelles are made from monomethoxy-poly (ethylene glycol)-S-S-hexadecyl (mPEG-S-S-C16), a hydrophobic material with improved solubility and stability in water. The presence of GSH causes the breakdown of the disulfide bonds, which triggers the release of the cargo. Additionally, the

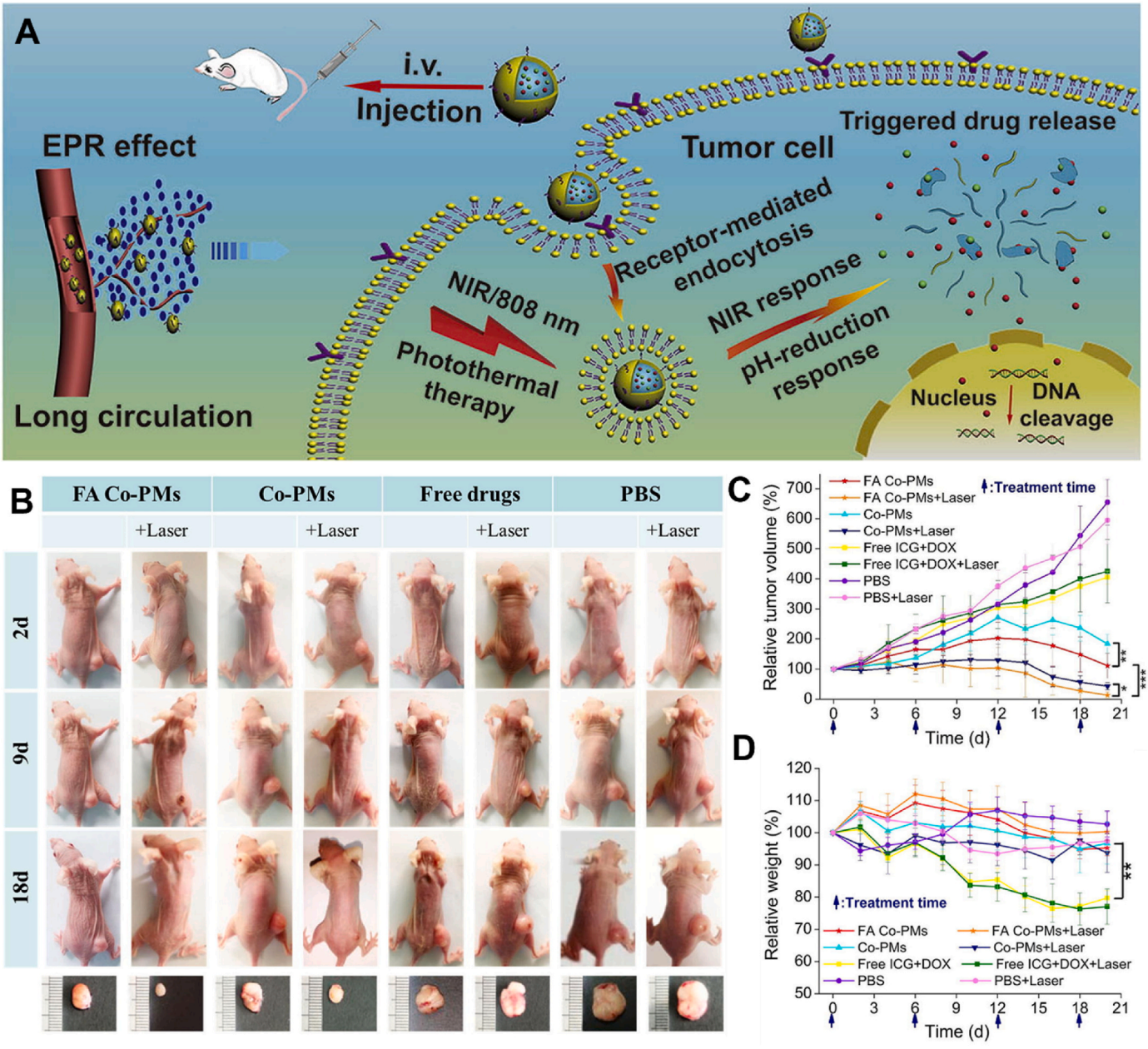

Fig. 9. (A) The application of micelles for DOX delivery and phototherapy ablation of cancer cells; (B) *In vivo* efficacy of nanostructures; (C) Tumor volume and weight upon application of micelles. Reprinted with permission from Elsevier (Zhang et al., 2018a).

combination of PCPDTBT dots and DOX provides both PTT and chemotherapy, effectively suppressing tumor growth (Cai et al., 2017).

In an experiment, three strategies were adopted to enhance the efficacy of micelles in chemotherapy. Firstly, DOX was combined with indocyanine green (ICG) to perform photothermal therapy (PTT) within the polymeric micelles. Secondly, the micelles were modified with folate to increase the uptake of nanocarriers through receptor-mediated endocytosis. Thirdly, the micelles were designed to be responsive to both pH and redox. A particle size of 100 nm with good monodispersity and high encapsulation efficiency was found to be the most effective for both DOX and ICG delivery. These micelles were uptaken by cancer cells via endocytosis, resulting in suppression of tumor development through a combination of chemotherapy and PTT (Fig. 9) (Zhang et al., 2018a).

7.2. Photodynamic therapy

An alternative method for PDT is the utilization of micelles. As previously stated, the mechanism behind PDT involves increasing the quantity of free radicals to damage cells. In this approach, Pluronic F127 micelles are altered with pheophorbide A and filled with DOX to form nanocarriers with a particle size of 146.5 nm and a zeta potential of −3.2 mV. Exposing these nanocarriers to light irradiation leads to enhanced ROS generation *in vitro* and *in vivo* to suppress tumor progression. In fact, nanocarriers provide both chemotherapy and PDT for melanoma suppression (Zhang et al., 2018b). Another approach to achieve both PDT and chemotherapy is the use of chlorin e6 (Ce6) micelles loaded with nitroimidazole (NI)-bearing polymers. These polymeric micelles, containing Ce6 and DOX, have a particle size of 138.5 nm and release their cargo when exposed to the hypoxic environment of a tumor. The hypoxic environment triggers the bio-reduction of the NI moiety, which transforms into an aminoidazole, leading to the disassembly of the micelle, release of the drug, and depletion of GSH. Upon irradiation, the NI is oxidized by Ce6, causing the collapse of the micelle and the release of the cargo, and generating aldehyde end-products, which in turn mediate both PDT and chemotherapy to suppress the growth of breast tumors (Deng et al., 2018).

NIR light is considered biocompatible with high tissue penetration for biomedical applications (Li et al., 2018a; Chen et al., 2012; Park

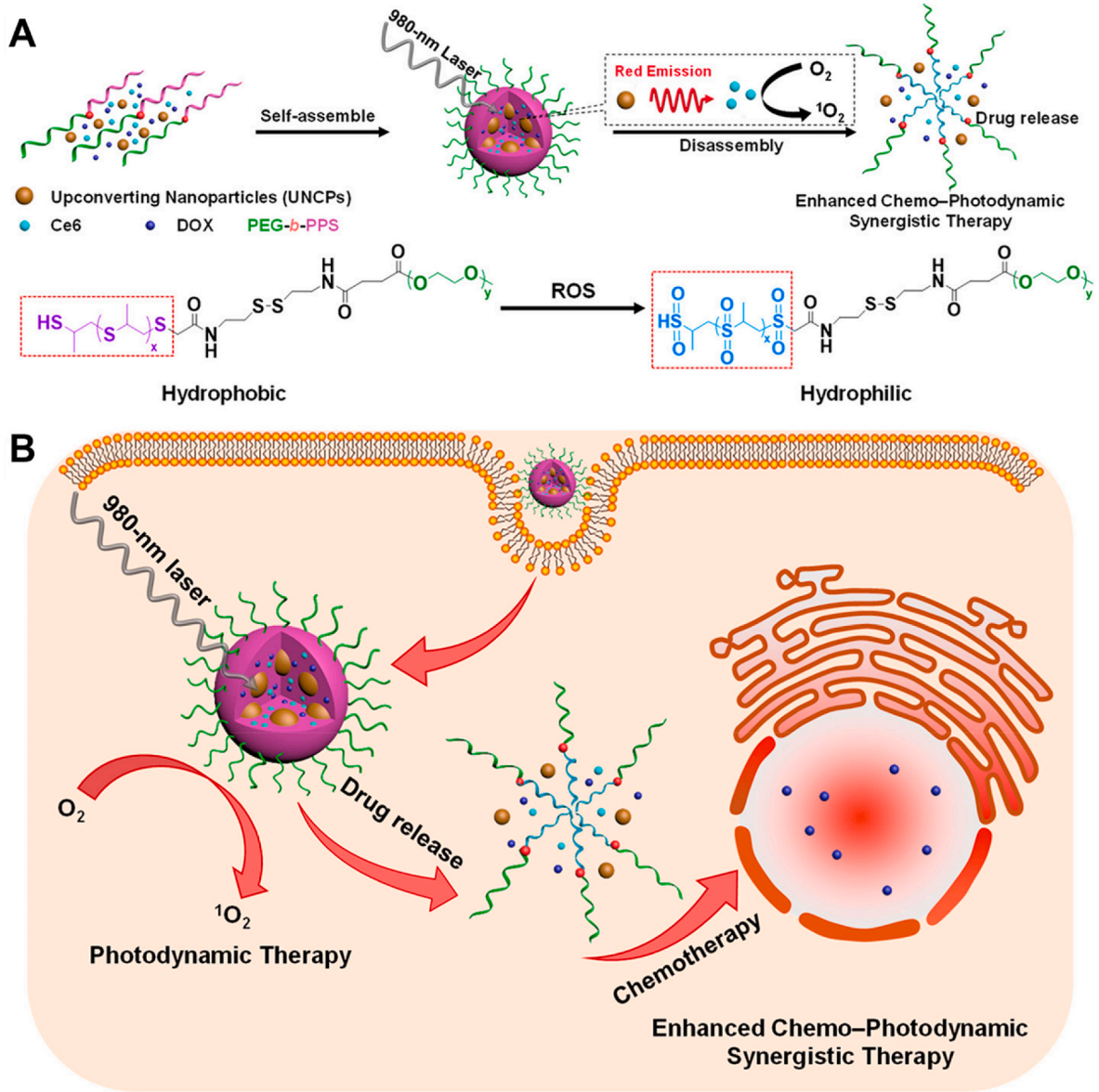

Fig. 10. (A) Synthesis of DOX-loaded micelles and their disassembly upon exposure to red emission; (B) Drug release upon irradiation and providing PDT in improving potential of DOX in cancer chemotherapy. Reprinted with permission from ACS (Chen et al., 2019).

et al., 2015). However, NIR has limitations in stimulating all photosensitizers, such as Ce6. Upconverting nanoparticles (UCNPs) to enable conversion of NIR to ultraviolet or visible light can be promising for biomedical applications due to narrow emission peak, high biocompatibility, and high photostability (Jalani et al., 2018; Chen et al., 2014b; Tian et al., 2013; Idris et al., 2015). The development of redox-sensitive hybrid micelles made of polymers and UCNPs has been explored for both photodynamic therapy and cancer chemotherapy. The hybrid micelles were formed by co-assembling UCNPs with block copolymers, followed by the loading of Ce6 and DOX. The UCNPs can convert near-infrared laser (980 nm) into visible light, inducing ROS generation through Ce6. This ROS generation not only enables photodynamic therapy for tumor cells, but also oxidizes poly (propylene sulfide) (PPS) to sulfoxide and sulfone, resulting in the release of DOX (Fig. 10) (Chen et al., 2019). Based on these studies, combination of PDT or PTT with chemotherapy is effective in improving the potential of DOX to suppress cancer (Table 4).

8. Surface-modified micelles

Tumor cells have different characteristics from normal cells, including differences in proliferation and metastasis as well as variations in receptor expression on their surfaces. Unlike epithelial cells which have low expression of folate receptors, the expression of these receptors increases in cells undergoing malignant transformation (Ramezani Farani et al., 2022). The functionalization of nanostructures has been performed in other studies for improving their potential in cancer therapy. After preparation of gold nanostructures, they were modified with PEG and then their functionalization with triptorelin were performed to enhance adhesion, affinity and selectivity towards triple-negative breast tumor cells (Uzonwanne et al., 2022). The iron oxide nanostructures were functionalized by a ligand targeting EGFR in suppressing progression of head tumor cells and such surface functionalization promotes cellular uptake in cancer cells (Freis et al., 2023). The modification of iron oxide magnetic nanoarchitectures with a cell-penetrating peptide improved their capacity of nanostructures in DOX delivery (Hasani et al., 2023). Hence, surface modification of nanostructures is a promising approach for targeted delivery of drugs. Folate receptor upregulation on the surface of cancer cells enables the import of folate into tumor cells for proliferation (Krais et al., 2014; Nosrati et al., 2022b). The use of folic acid modification in polymeric micelles has been successful in improving their selectivity towards tumor cells. P (MPC-co--MaPCL) polymeric micelles were created with folic acid modification for DOX delivery. These micelles had a spherical shape with particle sizes ranging from 90 to 140 nm. The intracellular accumulation of DOX in cervical cancer cells was increased by 4.3-fold and its cytotoxicity was enhanced as a result of the folic acid modification (Lu et al., 2019). It is also believed that PEGylation of micelles is effective in enhancing the blood circulation time of nanoparticles due to preventing protein interaction and clearance of micelles by MPS (Blanco et al., 2015; Harris and R.B.J.N.r.D.d. Chess, 2003). Besides, PEGylated micelles not only have a high circulation time in blood but also present with enhanced permeability and retention (EPR) effect (Mima et al., 2015; Stolnik et al., 2012; Maeda and Matsumura, 2011). However, frequent application of PEGylated micelles can lead to increased clearance from blood and immune system, negatively affecting their pharmacokinetic and biodistribution (Schellekens et al., 2013; Koide et al., 2008; Lila and KiwadaT.J.J.o.C.R. Ishida, 2013). Therefore, the use of folate-modified cell membrane-mimicking polymeric micelles is considered more effective for DOX delivery. These micelles are created from PMPC-based zwitterionic polymers that interact with folate receptors on cancer cell surfaces. For example, PCL-b-PMPC-FA micelles are biodegradable and can release DOX after a drop in pH from 7.4 to 5. These micelles have a particle size of 158 nm and exhibit high uptake in both breast and cervical cancer cells (Du et al., 2021). Therefore, when micelles are modified with folate, there is an increase in cellular uptake and cytotoxicity against tumor cells (Zhang et al., 2019b; Yang et al., 2013).

As a linear glycosaminoglycan, hyaluronic acid (HA) is a favorable compound for nanomedicine due to its biodegradability, biocompatibility, non-immunogenicity, and low toxicity (Shah et al., 2015). Hydroxy and carboxy groups are available functional groups for conjugation with other agents. CD44 is upregulated in many cancer types, and nanostructures can be modified with HAs to improve their tumor-targeting ability (Ashrafizadeh et al., 2021a). HA-modified polymeric micelles can be used for DOX delivery in combination with HA-glycyrrhetinic acid and HA-I-histidine conjugates. The anticancer activity of DOX-loaded micelles is examined in hepatocellular carcinoma, where they released DOX in response to pH and showed

Table 4
The role of micelles for delivery of DOX delivery to mediate phototherapy.

Nanovehicle	Cancer type	PDT/ PTT	Remark	Ref
Hierarchical micelles	Lung cancer	PTT	Enhanced internalization in cancer cells via endocytosis Hyperthermia induction Potentiating chemotherapy efficacy	Wan et al. (2014)
pH-responsive polymeric micelles	Cervical cancer	PTT PDT	Polydopamine nanoclustered micelles mediate PDT and PTT in reversing drug resistance	Xing et al. (2019)
Polymeric micelles	Cervical cancer	PTT	Enhanced drug loading efficiency due to presence of hydrogen bonds between urea/thiourea groups and drugs PTT-mediated drug release	Li et al. (2018b)
pH-responsive polymeric micelles	Cervical cancer	PTT	pH-responsive release of drug Combination of PTT and chemotherapy in synergistic cancer suppression	Jia et al. (2017)
NIR/GSH-responsive biodegradable micelles	Hepatocellular carcinoma	PTT PDT	119.7 nm particle size Low critical micelle concentration Photodecomposition Good biodegradation Controlled drug release	Zhang et al. (2019a)
Polymeric micelles	Cervical cancer	PTT	Efficient drug release High PTT efficacy Appropriate tumor ablation	Li et al. (2015a)
Polymeric micelles	Breast cancer	PTT	Development of pH- and redox-sensitive micelles High photothermal transformation efficiency Suppressing tumor metastasis	Wu et al. (2021)
Magnetic thermosensitive micelles	Breast cancer	PTT	Synergistic combination of chemotherapy and PTT in cancer suppression	Wu et al. (2016a)
Polymeric micelles	Cervical cancer	PTT PDT	Hyperthermia induction and increasing ROS generation Boosting DOX's efficacy in cancer suppression	Ji et al. (2022b)

significant cellular uptake in HepG2 cells owing to interactions of HA with overexpressed CD44 receptors (Wu et al., 2016b). It is noteworthy that micelles can be modified with two ligands for DOX delivery. By conjugating hyaluronic acid (HA) to folic acid (FA) through a redox-responsive disulfide bond, micelles are developed. The encapsulation efficiency of the micelles is excellent, with a particle size of 100–120 nm and a negative zeta potential of −31.5 mV. The release of DOX from the micelles is sensitive to redox conditions due to the presence of disulfide bonds and the HA and FA conjugates. This combination enhances the selectivity towards tumor cells and results in high cellular uptake rates (Yang et al., 2018b). In a separate study, redox-responsive HA–Fe-C14 micelles modified with HA were created for the delivery of DOX to the tumor environment. The addition of HA enhances the binding of the micelles to CD44 and enables drug encapsulation. The conjugation of HA to the micelles, along with the effects of GSH and electrostatic interactions, can lead to the release of DOX from the micelles (Fig. 11) (Mao et al., 2019).

One of the strategies for increasing the stability of DNA is its conjugation to peptide (Singh et al., 2010; Lou et al., 2016). Cationic peptides are located on the surface of DNA micelles and are effective for improving stability against degradation by nuclease digestion. Furthermore, modification of micelles with mucine-1 (MUC1) aptamers can increase recognition of tumor cells (Abnous et al., 2017; Taghdisi et al., 2016). In an effort, hybrid micelles were created from DNA blocks and used to deliver pro-apoptotic peptides DOX and KLA. The effectiveness of the delivery and internalization of micelles in breast cancer cells is improved by modification with the MUC1 aptamer and the combination of DOX and KLA for suppressing tumor growth (Charbgoo et al., 2018). Overall, modification of nanostructures with ligands is important and can lead to increases in the internalization of nanoparticles via endocytosis (Table 5) (Makvandi et al., 2021).

9. Conclusion and clinical implications

Nanomedicine has become a subject of significant interest in recent times due to its potential to enhance cancer management and treatment. While novel therapies such as drugs and genetic tools have been developed, their effectiveness is frequently limited because they lack specificity and targetability towards tumor cells. DOX is a commonly used chemotherapy agent in clinical practice, but its frequent administration often results in the development of chemoresistance. To overcome this issue, nanostructures can be employed to deliver low concentrations of DOX specifically to tumor cells, effectively bypassing the development of drug resistance. The biocompatibility of nanostructures is critical for their clinical utility, and lipid-based nanoparticles, including micelles, are considered among the most biocompatible nanostructures for cancer therapy.

This review investigated the function of micelles in the delivery of DOX for cancer treatment. Due to the unique features of the tumor microenvironment, micelles can be engineered as stimuli-responsive nanocarriers that can react to pH, redox, light, and other stimuli, allowing for better targeting of DOX to tumor cells. Furthermore, DOX can be co-delivered with other anticancer agents or genetic tools in micelles for more effective suppression of tumor cells. Surface modification of micelles using molecules such as folate, hyaluronic acid, and aptamers can improve their specificity towards cancer cells.

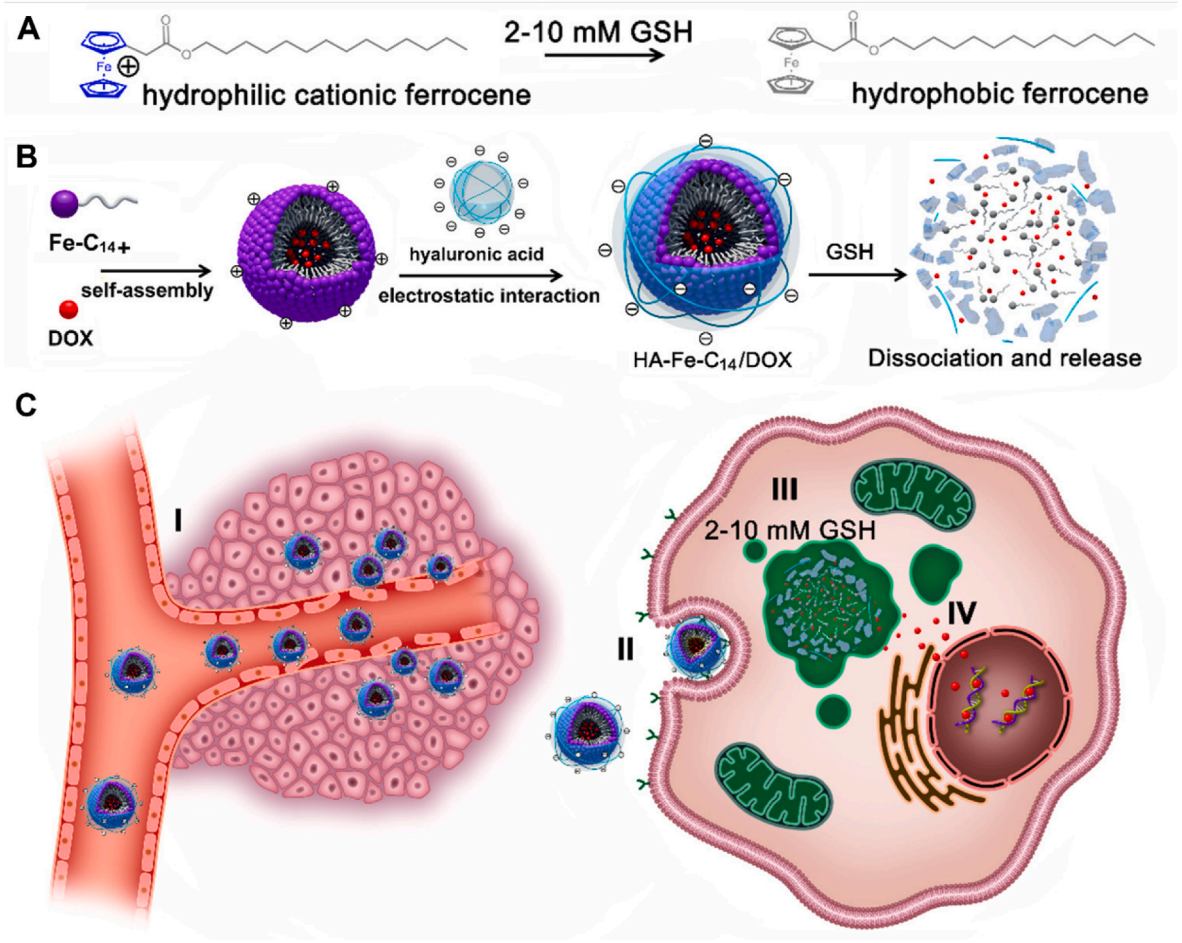

Fig. 11. (A–C) Development of DOX-loaded micelles for GSH-responsive release of DOX in cancer chemotherapy. Reprinted with permission from ACS (Mao et al., 2019).

Table 5
The surface functionalized micelles in DOX delivery.

Nanovehicle	Remark	Ref
Aptamer-conjugated and doxorubicin-loaded unimolecular micelles	Diameter of 69 nm pH-response and prolonged release of drug Enhanced cellular uptake Upregulation of caspase-3 and PARP Bcl-2 down-regulation	Xu et al. (2013)
MUC1 aptamer-targeted DNA micelles	CO-delivery of DOX and KLA peptide in suppressing breast cancer progression Increased penetration in tumor cells Decreased side effects	Charbgoo et al. (2018)
Aptamer-conjugated polymeric micelles	Suppression of pancreatic cancer Deep tumor penetration Increased cytotoxicity	Tian et al. (2021)
Aptamer AS1411 mediated Pluronic F127/ cyclodextrin-linked polymer composite micelles	Enhanced accumulation of DOX in tumor cells via endocytosis	Li et al. (2015b)
Folate-targeted polymeric micelles	Co-delivery of doxorubicin and SIS3 in suppressing chemoresistance	Wang et al. (2022c)
Folate-conjugated and pH-responsive polymeric micelles	Significant tumor internalization and targeting	Guan et al. (2017)
Isomeric folate-conjugated polymeric micelles	Ability of binding to folate receptors and suppressing tumor progression in animal model	Dong et al. (2014)
Thermosensitive and folate functionalized Pluronic micelles	Diameter of 35 and 50 nm Temperature-dependent release of drug Enhanced cytotoxicity against cervical cancer	Yang et al. (2013)
Folate-targeted dextran/ retinoic acid micelles	Particle size of 82.86 nm Zeta potential of −4.68 mV Drug loading efficiency of 96%	Varshosaz et al. (2014)
Stimuli-responsive, dual-function prodrug encapsulated in hyaluronic acid micelles	Reducing P-gp expression to overcome chemoresistance	Qiu et al. (2022)
pH-Responsive Hyaluronic Acid-Based Mixed Micelles	pH-sensitive release of drug and ability in suppressing hepatocellular carcinoma progression	Wu et al. (2016b)
Reduction-sensitive CD44 receptor-targeted hyaluronic acid derivative micelles	Encapsulation efficiency of 88% Diameter of 100–120 nm Zeta potential of −6.7 to −31.5 mV Cellular uptake via CD44-mediated endocytosis	Yang et al. (2018b)
Chitosan coated pH/redox-responsive hyaluronic acid micelles	Co-delivery of doxorubicin and siRNA-PD-L1 in breast cancer immunochemotherapy	Song et al. (2022)
Zwitterionic pH-responsive hyaluronic acid polymer micelles	Internalization in tumor cells via CD44-mediated endocytosis	Gao et al. (2019)

Additionally, using micelles in photodynamic therapy and photothermal therapy can improve the effectiveness of DOX in cancer chemotherapy. In conclusion, micelles show great promise for cancer treatment, and future studies should concentrate on their clinical translation to benefit cancer patients.

The concept of this paper has been organized in a manner to develop smart nanocarriers for delivery of DOX as a popular drug in chemotherapy. The idea has been evolved in a way not to mediate its delivery, but propose ideas about designing smart micellar nanostructures for DOX delivery. The advantageous of using micelles is that they mediate sustained delivery of DOX and increase its accumulation in cancer cells. Moreover, the functionalized micelles increase cellular uptake compared to non-modified micelles. Furthermore, stimulus-responsive micelles release DOX at tumor site. Another benefit is that micelles mediate co-delivery of DOX with other drugs and genes in cancer therapy. The third benefit is that micelles induce PDT and PTT in increasing potential of DOX in synergistic cancer removal. The most important benefit that can pave their application in clinical trial is their high biocompatibility. However, one of the disadvantageous of micelles is their degradation and burst release of drug that can be solved by modification through chitosan or other polymers to prevent burst release of drug and improve potential in cancer therapy.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.115722.

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