Application of Polymeric Micelles for Cancer Treatment: A Review

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Abstract. Polymeric micelles have been considered a promising development in chemotherapies to treat cancer diseases in recent decades. Bearing a structure of hydrophilic outer shell and hydrophobic core, these micelles possess many advantages like their nano-size structure, self-assembly synthesis, physical and chemical stability, biocompatibility, prolonged blood circulation time, and high drug loading and release capacity. The increased availability of building block copolymers that produce polymeric micelles also enables researchers to create the ideal drug delivery system. The formation of these polymeric micelles depends on various non-covalent interactions, the used concentration and temperature, block lengths, and methods of preparation. Among these polymeric micelles, stimuli-sensitive micelles have been developed and begun to attract more attention in recent years for their high on-site specificity and enhanced drug release efficacy. To accommodate the complex microenvironment in tumors, such as the internal changes in pH, reductive responses, and enzyme activities, or the external factors like visible lights, UV irradiations, and temperature, the stimuli-sensitive micelles exhibit strong stability, high drug loading, efficient drug delivery, specific site release, and mild side effects in recent studies. This research also discusses dual or multi-stimuli-sensitive polymeric micelles that are under high research nowadays, dictating a more novel and efficient way of cancer treatments and clinical practices.

Keywords: Polymeric micelles; cancer treatment; stimuli-sensitive micelles; application.

1. Introduction

Nowadays, anti-cancer treatment has grown to become a significant issue for scientists and physiologists because of the rapid cells' abnormal growth and the possibility of invading other parts of the human body caused by cancer diseases. Cancer has been deemed one of the most complex diseases because it is not a single disease but a combination of a group of diseases. Many types of cancer show different and distinct characteristics and chemical properties. Various treatments are performed to treat cancers, but cancer would still not be cured completely. Among all cancer symptoms, the tumor has become the most obvious one and attracted scientists' attention starting from the twentieth century. In this case, tumor heterogeneity has received the most attention and effort because of the diverse microsystem in the human body, such as pH, temperature, hydrophobicity, cell and enzyme activities, etc. Due to host variabilities such as gender, age, and genetics, the solid tumor will be affected by these factors and genetic mutations, which will thus exhibit heterogeneity. Consequently, the essential goal of treating tumor heterogeneity and cancers will be successful and effective drug delivery in the human body.

How to deliver the anti-cancer drugs to accommodate the diverse human body system has become the primary objective in the pharmaceutical field. Previous research has shown the success of using nanoparticles in treating diseases. One of the most typical ones is the monoclonal antibodies (mAbs) which have been proved to be the effective drug carriers for active drug targeting. Further studies have shown that mAbs lack penetration in entering solid tumors [1]. Therefore, mAbs were not considered a successful candidate for cancer treatment. In the late twentieth century, nanoparticles have been developed and researched to overcome these difficulties because they could solve the problems caused by undesired side effects and physical responses of traditional drugs and drug-delivery systems. Nanoparticles showed high stability and ease in the formulation. They could be used successfully in the human body and harsh environments. The most crucial part of nanoparticles is their nano-scale size since traditional drugs are large in size, making it extremely difficult to either

directly enter or penetrate the solid tumors. However, this will be overcome easily by nanoparticles; thus, these nanoparticles will be considered a more effective candidate for drug carriers.

Among all the nanoparticles, polymeric micelle has recently continued attracting scientists' attention to a large extent. Polymeric micelles are self-assembled polymers with a unique amphiphilic structure. Because of polymeric micelles' physical and chemical characteristics, they will become a better candidate in the pharmaceutical area, especially for cancer treatment. Polymeric micelles are tiny in size, usually below 100nm. It will be much easier for them to penetrate the solid tumor and enter the human body. Their small size will have a narrower distribution when presenting in human blood vessels. Thus, they could avoid blocking the circulation system or aggregation during transport. The polymeric micelles could also be chemically modified to obtain certain desirable functional groups for specific purposes.

One of the most useful chemical treatments is the inclusion of polyethylene glycol (PEG). By adding PEG, the adhesion of opsonin could be reduced to some extent and thus help to increase the polymeric micelles' long-term circulation time in the human body [1]. Because of their nano-scale size and the increased circulation time, drug payloads in tissues could also be expanded to improve drug accumulation in tumors rather than in other off-site areas. Polymeric micelles are proved to have better stability both physically and chemically. For example, when presenting in the human body where pH and the temperature are sensitive, they will maintain their original properties without damage. Some polymeric micelles are synthesized as pH or temperature-sensitive, so this property will make it easier for these sensitive polymeric micelles to load and release drugs when intentionally or unintentionally changing the surrounding environments.

As discussed above, polymeric micelles have an amphiphilic structure. Due to the aqueous environment in the human body, polymeric micelles could become suitable carriers for hydrophobic drugs since these drugs can stay in the inner core with more solubility, and the hydrophilic outer shell will help the drug carrier-drug system enter the human body more readily. For the polymeric micelles to maximize their compatibility with different drugs and complex solid tumors or cancer diseases, more chemical treatments should be conducted to improve the performance of these polymeric micelles. Moreover, how to control the conditions to formulate an effective micelle with different functional groups has become another critical goal in drug delivery. Additionally, because of the complex microenvironments in tumors and cancer sites, how to maximize the drug loading capacity and release specificity has also become another essential objective in this research.

2. Formation of polymeric micelles

Polymeric micelles are becoming increasingly attractive and promising for their novel drug delivery abilities. Polymeric micelles usually have spherical amphiphilic structures. By nature, they possess a hydrophilic shell or corona, which can help micelles accommodate the aqueous environment. A diagram of the copolymers and the polymeric micelles is shown in Fig.1. Because of the hydrophilicity of the shell, it can be used to stabilize the micelles through the reticuloendothelial system (RES). The inner core, on the contrary, is hydrophobic, which can help encapsulate hydrophobic or poorly-water-soluble drugs. As discussed above, the copolymers that make up the micelles always contain nonionic water-soluble and other ionic segments, promoting the formation of a hydrophobic core through neutralization of oppositely charged surfactants. For instance, the polyion complex micelles can be synthesized based on the reaction between PEG-g-pAsp and the surfactant (that is, CTAB) in H2O [2]. In this work, the results showed that the CTAB could neutralize the carboxyl groups to form a hydrophobic core to maintain higher stability, allowing the prepared polyion complex micelles to become a good candidate for drug delivery systems.

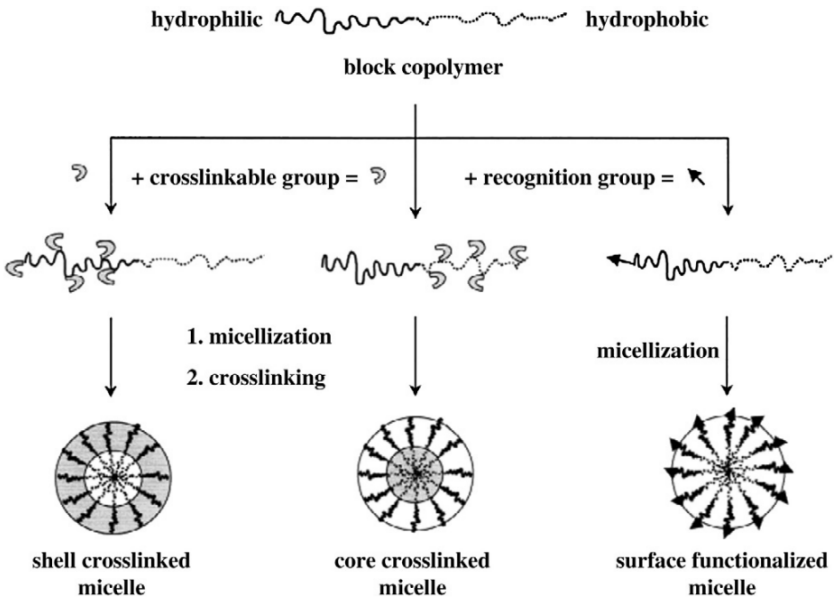

Fig. 1 Types of amphiphilic copolymer and mechanism of formation [3]

Because hydrophobic drugs still have to maintain enough hydrophobicity to enter the hydrophobic cell membranes and sustain sufficient affinity with the target receptors, anticancer drugs could be encapsulated in the inner hydrophobic core of the amphiphilic copolymers to target the hallmarks. To prepare polymeric micelles, amphiphilic diblock copolymers are most commonly used, along with triblock copolymers and graft copolymers. The reason for using different copolymers is that they possess different chemical and physical properties, which could add functional groups to the polymeric micelles to achieve the desirable effects. For example, in the drug delivery system to combat cancer cells, circulation time, drug release, and targeting moieties are all significant factors to consider. Thus, the functions of polymeric micelles are under increasing development. In this case, the hydrophilic outer shell mainly comprises polyether. Increasing the chain length of PEG could help make the hydrophilic shell denser, increasing the stealth properties of polymeric micelles and the circulation time *in vivo* [4]. These hydrophilic copolymers can help provide stealth properties to polymeric micelles, which will prevent the uptake by the RES and extend the blood circulation time. Besides, triblock copolymers like Pluronic are also used, which generally have a structure of $PEO_{m/2}$-b-PPO_n-b-$PEO_{m/2}$ [3]. Alakhov et al. showed in their study of MDR tumors that by using Pluronics p85 copolymer, the efflux action of P-glycoprotein was inhibited to some extent and thus affected the multi-drug resistance, enhancing the activities of antineoplastic agents against MDR tumors [5].

The formation of the polymeric micelles depends on the non-covalent interactions, mainly attractive and repulsive forces, between different polymers. The attractive interactions include the hydrophobic effects, electrostatic attractions, and complexations, while the repulsive interactions include the steric interactions, electrostatic repulsions, and hydrations [6]. Because of these non-covalent interactions, polymeric micelles will stay at a specific size and will not grow at an unlimited rate. However, during the formation process, there are many factors to consider to render an efficient and function-desired polymeric micelle. Letchford et al. discussed two main factors influencing the micelle formation–block length and methods of preparation [7]. When the hydrophilic blocks have a greater molecular weight (MW) than hydrophobic ones, the copolymers will easily be self-assembled into tiny monodisperse micelles. When the hydrophobic part has an MW approaching or exceeding the hydrophilic component, it will be hard for the copolymers to self-assemble by direct dissolution. Riley et al. synthesized the polymeric micelle using MePEG-b-PDLLA building block with constant MW of MePEG and changing MW of PDLLA [8]. The results demonstrated that the MW of the used PDLLA could be used to regulate the formation of micelles. The ^{1}H NMR and ^{13}C solid-state NMR were used to analyze the state shifts of the MePEG and PDLLA [9]. The result of the ^{1}H NMR showed that there was a disappearance of methyl hydrogens and a doublet-doublet peak, which indicated that

at the interface of MePEG and PDLLA, there was a more mobile phase. And the ^{13}C NMR further confirmed that no matter the molecular weight of the PDLLA, there appeared two phases, that is, the solid-like core and the mobile interfacial area.

In addition to influencing the physical state of the micelles, the hydrophobic and hydrophilic block length ratio can also affect the morphologies of the resulting particles. Discher et al. studied the PEG-PBD and PEG-PEE copolymers under different ratios of PEG (f_{EO}), where the f_{EO} was also used to tune the morphology of the copolymers [10]. And by controlling the ratio between hydrophilic and hydrophobic compartments, the resulting molecular shape will become either cylinder, wedges, or cones, dictating the final morphology: membrane, rod-like, or spherical structure [10] [11]. The second factor that affects micelle formation is the methods of preparation. When reaching the critical micelle concentration (CMC) threshold, both the surfactants and the copolymer building blocks start to self-assemble. When presented in aqueous solutions, the poorly soluble drugs will be encapsulated into the micelles, thus forming a drug loading and delivery system. In this case, the drugs will spontaneously be encapsulated into the self-assembled micelles. After reducing the pressure, the organic solvent evaporates, leaving a polymeric micelle solution. Kedar et al. also summarized the methods of synthesis, methods of micellization, and drugs encapsulated of several common polymers [3].

3. Application of different stimuli-sensitive micelles

Because of the advantages of nanoparticles and the polymeric materials, they have been deemed good candidates for chemotherapy in recent years. However, conventional chemotherapy methods still possess many defects, such as off-target drug release and low efficacy of release in the target site [4]. In this case, in recent decades, newly emerged nanoparticles and polymeric micelles have increased attention and are more widely used in chemotherapy combined with radiotherapy in the medical field. Among these nanoparticles, stimuli-sensitive polymeric micelles have become the most promising because they are able to respond to both intercellular and extracellular stimuli and then release drugs by changing their micellar structures. As a result, these stimuli-sensitive polymeric micelles could lower the possibility of off-site drug release and are able to release drugs in various microenvironments. The mechanism of stimuli-sensitive micelles could be divided into four main categories: pH-sensitive, thermo-sensitive, redox-sensitive, and light-sensitive.

4. pH-sensitive micelles

The first and currently widely used stimuli-sensitive polymeric micelles are the pH-sensitive micelles. When presenting in low extracellular or intercellular pH microenvironments, the structure of these micelles will be degraded, thus promoting the release of anti-cancer drugs. The mechanism of pH-sensitive micelles could be divided into two strategies. The first strategy uses pH-dependent degradable linkers between the hydrophilic/hydrophobic copolymers to construct the amphiphilic polymeric micelles. In this case, when the micelles reach tumors or lysosomes that are low in pH, the linker will degrade rapidly and cause the disassembly of these polymeric micelles, resulting in inner-encapsulated drug release [12]. For the hydrazone linkers, there will be acid-labile hydrazone bonds, which could not only provide the required hydrophobicity for the self-assembly of micelles but also provide the ability to release drugs facing low pH environments. For example, the paclitaxel-polymer pro-drug micelles were prepared according to the existing literature [13]. In a low pH environment (pH=5.0), these pH-sensitive polymeric micelles degraded rapidly, releasing the PTX that helped treat breast cancer cells. The second strategy, such as adopting pH-responsive building blocks, can promote drug release and endosomal escape by altering the outer charges to degrade the structure of polymeric micelles under low pH environments. Bae et al. prepared a new copolymer, and the result showed that below pH 7.4, there appeared to be strong ionization of pHis block copolymeric micelles, leading to a sharp increase in drug release [14].

Based on these principles, Lei et al. recently prepared a novel drug carrier POEGMA-b-P(ABMA-co-AMA) (POPAA), to deliver drugs in anticancer treatments [15]. As shown in Fig.2a, particle size and PDI of POPAA practically did not change, indicating high stability of physical shape. As shown in Fig.2b, the zeta potential ranged from -4.37mV to +5.21mV, indicating that M(DNR) could maintain negative charges to avoid the removal of RES. And in Fig.2c, the results showed that DNR release was less than 13% at pH 7.4, about 22% at pH 6.5, and 73% at pH 5.0, respectively. These numerical results indicated hydrolysis of imine bonds in acidic conditions, which led to the destruction of polymeric micelles. The percent-release further supported the success of using pH-sensitive micelles in anti-tumor treatment.

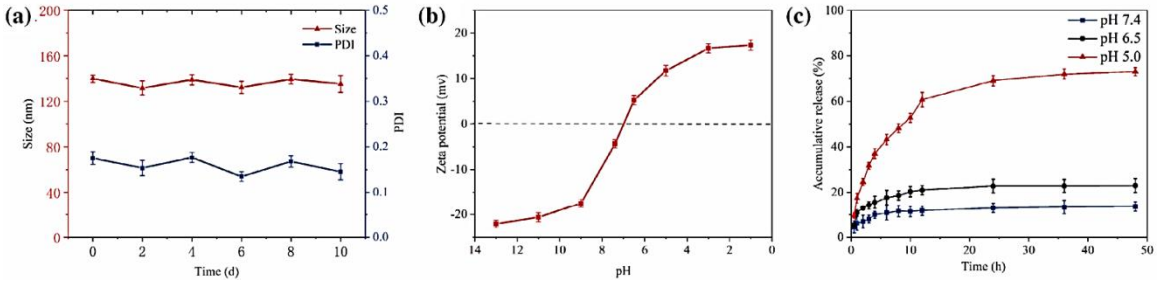

Fig. 2 Characteristics of M(DNR): (a) in vitro particle size and PDI stability, (b) zeta potential of POPAA concerning changes in pH, and (c) DNR release from M(DNR) during 48h [15]

5. Thermo-sensitive micelles

Another stimuli-sensitive micelle widely studied and adopted in recent years is the thermo-sensitive micelles, which can respond to the relatively high temperature in tumors or the inflammation regions, and thus successfully and effectively release anti-cancer drugs in such areas. In this case, poly (N-isopropyl acrylamide) (pNIPAAm) and its derivatives are widely used as the outer shell of the thermo-sensitive micelles due to passive targeting and thermo-sensitivity [16]. Due to the different temperature environments in the human body, the balance between the hydrophobic and hydrophilic parts of the thermo-sensitive micelles can be modified, such as conjugating to other block polymers, changing the chain lengths, and altering the degree of substitution, to accommodate more specific diseases or cancer sites. For example, Zhao et al. prepared temperature- and pH-sensitive crosslinked micelles [17]. The results demonstrated that these resulting micelles could successfully load Dox in their hydrophobic core and remained stable at average body temperature at pH=7.4. However, when the temperature reached LCST (39℃), the micelles de-structured to a large extent and thus successfully released Dox. Additionally, in developing thermos-sensitive micelles, poly (propylene glycol) (PPG) is also widely utilized by linking to PNIPAAm. By changing the balance between the host molecule (pNIPAAm) and guest molecule (PPG), the deformation behavior of these thermo-sensitive micelles could be easily tuned and promote drug release [4]. Besides, in recent years, dual or multi-stimuli-responsive micelles have been researched and used to enhance the drug-delivery system further. For instance, at lower pH (6.5), pGlu will transform from coil to helix structure, facilitating the aggregation; at a temperature above LCST, phase transition of these dual stimuli-sensitive micelles will also occur simultaneously. In this case, drug delivery efficiency and on-site specificity could be achieved more easily.

Besides these thermo-sensitive micelles discussed above, Long et al. developed a novel dual drug delivery system using thermo-responsive polymeric micelles capped mesoporous silica nanoparticles (MSN) [18]. In this system, when the temperature was elevated to above LCST, the FP250 could undergo a sharp shrinkage and simultaneously extrude the drugs. With a high concentration of glutathione (GSH) stimulus, MSN could also promote drug release under low pH conditions. The group's results are shown below in Fig.3a that the CMC value of MSFP250 was 20.7μg/ml, designating good stability in the dilute condition of the drug delivery system. Besides, according to Fig.3b, in the absence of GSH, very few amounts of Dox were released that could be negligible,

indicating FP250 could also become a "gatekeeper" that prevented the premature drug release. In contrast, when 10mM GSH was added, a sharp release of Dox appeared; the percent of release increased as the pH of the system reduced from 7.4 to 5.0 and when the temperature increased from 37℃ to 40℃, resulting in a maximum (around 61%) drug release at low pH (5.0) and hyperthermia (40℃).

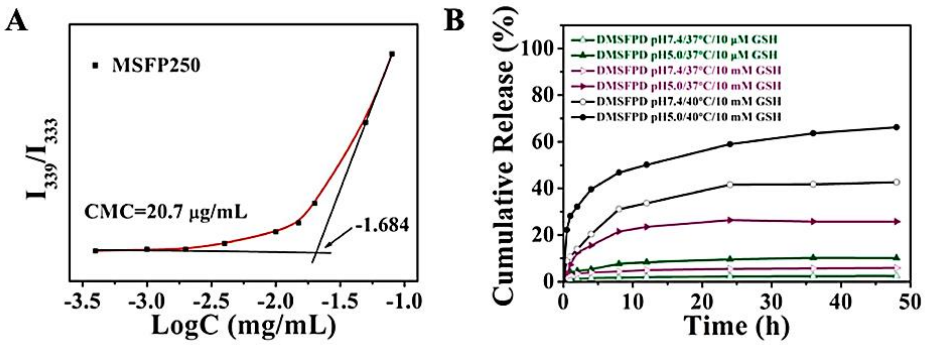

Fig. 3 Characteristics of DMSFPD: (A) critical micelle concentration curve, (B) drug release from DMSFPD under different conditions [18]

6. Redox-sensitive micelles

Redox-sensitive polymeric micelle is another stimuli-sensitive nanoparticle. The mechanism of redox-sensitive micelles lies in that the disulfide bonds in these micelles will cause the degradation of the micellular structure when the concentration of intracellular glutathione changes, inducing the release of anti-cancer drugs. In the human body's cytosolic compartments, the glutathione (GHS) concentration is approximately 1-10mM, much higher than that in plasma (2μM). Additionally, GHS concentration in tumor issues is even about 4-fold higher. Therefore, these nanoparticles containing disulfide bonds will be broken down in the tumor microenvironment and the intercellular compartments, promoting effective drug release. Based on these principles, anticancer drugs like tioguanine and gemcitabine are often conjugated with PEG-based copolymers through disulfide linkage, showing good reduction sensitivity. Besides, hyaluronic acid (HA) is also utilized as another redox-sensitive biopolymer [19].

Xu et al. synthetized redox-responsive oridonin (ORI) polymeric prodrug micelle (P-ss-ORI) to achieve cancer treatment [20]. The CMC, particle size, and drug loading capacity of developed self-assembled micelles are ~10mg/L, ~80nm, and 18.7%, respectively, indicating that they could be used as an effective drug carrier for the treatment of cancer. To this end, the anti-cancer effects of this redox-sensitive micelle *in vivo* were further analyzed. The result in Fig.4a-f showed that P-ss-ORI was very effective in tumor suppression with a TSI of 89.3%, better than either free ORI or P-ORI. The result in Fig.4g showed that the body weight of mice practically did not change, indicating minimal side-effects of using ORI in cancer treatment. In this work, the used ORI shows considerable potential and promise in advanced gastric cancer (GC) tumor inhibition and provides different strategies for cancer treatment in the future.

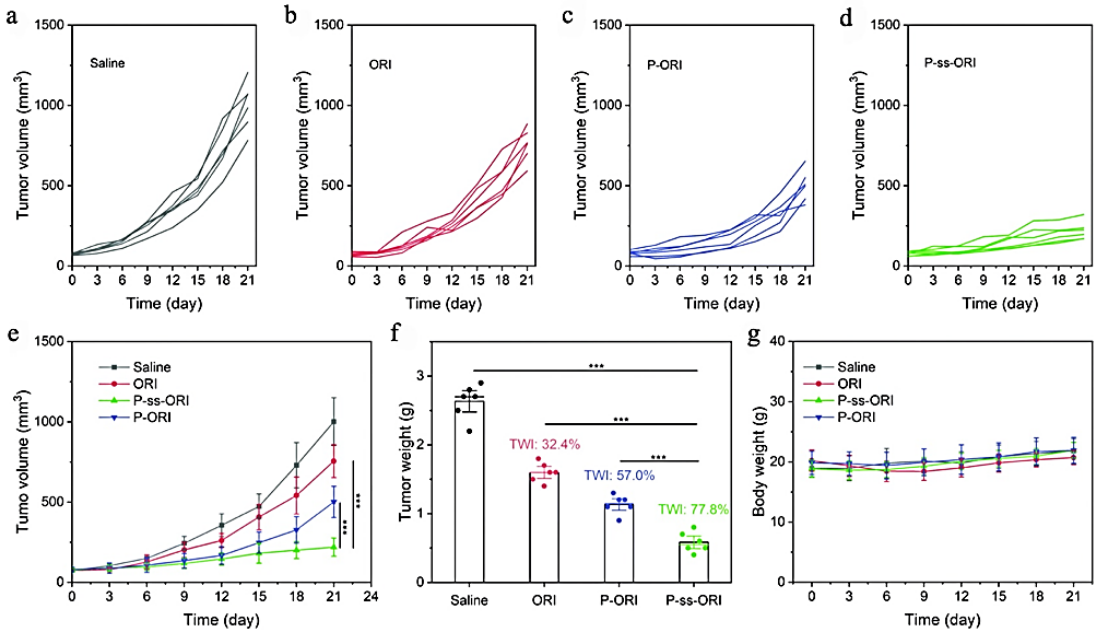

Fig. 4 *In vivo* results of saline, free ORI, P-ss-ORI, and P-ORI [20]

7. Light-sensitive micelles

The last category of the four stimuli-sensitive micelles is the light-sensitive micelle which is responsive to the near-infrared (NIR) lights. By loading the NIR-responsive chemical entities or chemotherapeutic agents, and when presenting under irradiation and induced rising temperature, the structure of these light-sensitive micelles will be degraded and thus release the encapsulated drugs [4]. Compared with UV-mediated degradation, visible light-sensitive micellular degradation has more advantages, such as BODIPY. When exposed to visible light irradiation (470-490nm), the B-O bond in BODIPY will degrade, separating the hydrophilic and hydrophobic parts of the self-assembled micelles and thus, the drugs could be released successfully. Moreover, 1O2-sensitive moieties are also very often utilized under visible irradiation where PEG and PCL blocks are linked by 1O2-breakable vinyl dithiol double bonds, which will form dioxetane intermediates that are readily cleaved. However, to activate the degradation of these light-sensitive micelles, light-mediated photodynamic therapies, such as using photosensitizer Ce6, are needed to generate the singlet oxygen.

Deng et al. used a two-step irradiation strategy to disrupt singlet oxygen-responsive polymeric micelles to promote photodynamic anti-cancer therapy [21]. In this case, through the dual irradiation process, the light-sensitive micelles would first break apart after a short time of irradiation to promote the release of Ce6 into the cytoplasm. Then, after 2 hours, the second long-time irradiation will generate more 1O2 to kill the cancer cells much more efficiently. They performed in vivo experiments to test the efficacy of this dual-step irradiation, as shown in Fig.5, where the mice were divided into six groups after their tumor size reached 100mm3. The results illustrated that the average tumor volume (RTV) for the dual-step irradiation was 2.02, much lower than that of the PBS group (9.64). Besides, the therapeutic effect was significantly enhanced for the dual-step irradiation, with TIR reaching 88.1%, far higher than the 54.1% TIR of the single-step method. After measuring the body weight of these mice every two days after the injection, there appeared practically no weight loss, indicating fewer side effects of this cancer treatment.

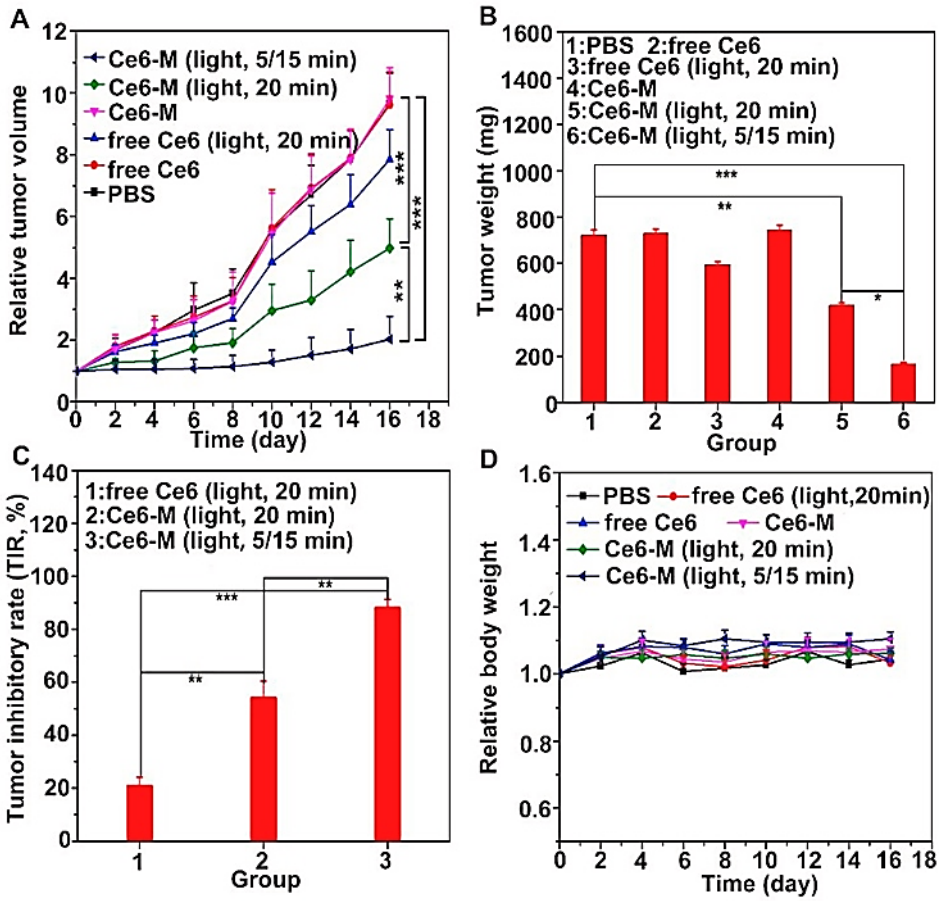

Fig. 5 *In vivo* test results of dual-step irradiation [21]

8. Conclusion

In recent years, polymeric micelles have been developed into promising and efficient nanocarriers in the drug delivery system. Because of their amphiphilic structure, the synthesis of polymeric micelles depends primarily on balance between hydrophilic and hydrophobic copolymer building blocks, in which the combination of conjugation has shown great possibilities and potential. In this case, for the past few decades, scientists have been developing ideal polymeric micelles that possess an excellent capacity for drug loading and release in anti-cancer treatments. This research focuses on the main categories of polymeric micelle forming mechanisms and recent trends in choosing more suitable polymers blocks to enhance the therapeutic performance. Additionally, stimuli-sensitive micelles manifest huge potential in cancer treatment as they exhibit high efficacy and on-site specificity. These stimuli-sensitive micelles can respond to internal environments in solid tumors like pH, temperature, and reductive conditions, as well as external stimuli like light irradiations. Combining different stimuli-responsive compartments, the multi-sensitive micelles could further improve the drug loading and release efficacy to a large extent. The results of the most recent studies listed in this research have proved the success and feasibility of using these multifunctional micelles as the loading capacity and TIR increased significantly compared with free anti-cancer drugs or single functional micelles.

However, in creating an optimal drug delivery system, there are still many challenges, such as a decrease in blood circulation during the loading of drugs in the micelle core, difficulties in controlling kinetic stability and kinetics in degradation, problems in delivering drugs in the intercellular compartments, and hardness in determining the ideal balance between polymeric building blocks in vivo. Nevertheless, despite these challenges, multi-sensitive micelles still are extremely promising and efficient drug carriers in chemotherapies and clinical fields. Future research on developing the

optimal polymeric micelles will further transform these advantages into practical usage to maximize the recovery rate of such diseases.

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