Application of Polymer Micelles in Medical Field

Yuqing Wu*

School of Materials Science and Engineering, Beijing University of Chemical Technology, Beijing, China

*Corresponding author: 2019020327@buct.edu.cn

Abstract. Compared with other polymer materials, the synthesis and application of polymer micelles have received more and more attention. Polymer micelles have been exploited as nano-pharmaceutical vectors in a range of medical areas recently because of their distinct benefits, including high targeting, strong biocompatibility and low toxicity. Polymer micelles are based on the physiological conditions of the package of drugs, the release of drugs under specific conditions, and to achieve the purpose of drug targeted release. This research discusses the types and formation mechanisms of polymeric micelles. And the application performance of polymer micelles in medical fields is further analyzed, such as for drug and gene delivery delivery, tumor imaging, and vaccine design, which also provides a reference for the development and application of polymer micelles in the future.

Keywords: Polymer Micelles, Medical Application, Tumor Treatment.

1. Introduction

Polymer-based nanomaterials mainly include hyperbranched polymers, liposomes, polymer micelles and nanogels. Among them, micelles are polymer-based nanomaterials that are widely used as biomaterials. When amphiphilic block copolymers are introduced into aqueous environment, they self-assemble to create polymer micelles, which are nanoadjugates with shell/core architectures [1]. Its hydrophobic core can encapsulate a range of hydrophobic anticancer medications without changing their chemical structure, improving the stability and solubility of the drugs. Hydrophilic shells and nanoscale particle sizes contribute to the release and enrichment of drugs *in vivo*. However, the micellar carrier is sensible to the effect of the inner environment, and will cause problems such as early release of drugs and drug resistance due to structural damage occur.

Polymer micelles (polymeric micelles, PMs) have a special biphilic core-shell structure. The core is hydrophobic, which can be encapsulated hydrophobic drugs. And the shell is hydrophilic, which can carry hydrophilic drugs. Good biosafety and biocompatibility, a certain degree of reduction of toxic side effects and other characteristics are widely used in the medical field. However, polymer micelles still have certain limitations in their applications, such as the lack of stability in PMs and the slow release of drugs. As a result, it has become very urgent to develop new synthetic methods for polymer micelles or to introduce other functional components to modify the physicochemical properties of polymer micelles. Amphiphilic block copolymers make up polymeric micelles, which in an aqueous medium will self-assemble into micelles with hydrophobic core. The hydrophilic shell prevents micelles from aggregating and settling, while also protecting therapeutic drugs, and the hydrophobic inner core binds the micelles together and wraps around insoluble molecules. The most frequent types of polymer micelles are di-block copolymers or tri-block copolymers comprising hydrophilic and hydrophobic blocks. Polymer micelles utilize block copolymers to deliver therapeutic drugs, such as nucleic acids, small molecule drugs and proteins [2]. As a result, according to the various characteristics of each therapy, block copolymers' intended physicochemical attributes will change. As are frequently the case, hydrophobic small molecule medications can be physically wrapped into the hydrophobic nucleus of the micelle by loading them in amphiphilic block copolymers containing hydrophilic and hydrophobic blocks. At the same time, biopolymers such as proteins and nucleic acids often need to bind to polymer micelles in the form of electrostatic interactions [3].

Considerations of biological interactions must take into account the hydrophilic shell which protect the drug for the polymer micelles. By reducing the binding of serum proteins and complement systems that protect encapsulated drugs, biocompatible hydrophilic blocks can prevent drug loss during the body's circulatory system. Otherwise, plasma protein can easily absorb polymer micelles causing them to clear from the body, and therefore, resulting in the entire polymer micelle, along with the drugs in it hydrophobic core, being cleared by the reticuloendothelial system (RES) [4]. In order to avoid this elimination, the introduction of hydrophilic block copolymers that make up the polymer micelle can confer high biocompatibility on the polymer micelles. Common hydrophilic polymers include polyethylene glycol (PEG), poly (2-oxazolidin) (Pox), glucose, heparin, chitosan, hyaluronic acid and chondroitin sulfate. Drugs that are insoluble are dissolved in the hydrophobic core of polymer micelles by hydrophobic blocks, which also keep track of the drug discharge from the micelles [5]. The core of the polymer micelle has a hydrophobic environment, and the hydrophobic interaction forces promote the dissolution of the insoluble drugs in the hydrophobic polymer micellar core consisting of hydrophobic blocks. This interaction helps to retain the drug in the hydrophobic core and controls the progressive release of the encapsulated drug into the external environment. Also, other molecular interactions in the hydrophobic core include hydrogen bonds and π - π interactions, which can enhance molecular interactions between hydrophobic blocks and insoluble drugs [6]. Common hydrophobic polymers include polyethers, polyesters, polysaccharides, etc.

Due to their unique capacity to control drug administration by internal chemical or external physical stimuli, block copolymers with stimulus response capabilities have drawn a lot of attention as materials for polymer micellar designs. When stimulus reactive block copolymers are exposed to chemical stimuli such as redox, pH, hypoxia, enzyme or physical stimuli such as light and temperature, the properties of the block copolymers change following, which facilitates the regulation of the drug delivery function of polymer micelles, such as monitoring the drug accumulation at the lesion site or the quantity of drug discharge. The physical and chemical properties of pH-stimuling polymers can be adjusted by changes of pH values in certain environment, thereby controlling drug release at the target location. For example, the tumor's endosomes and local pH values are slightly acidic, so TME is the target location for this pH-sensitive polymer. Temperature-responsive hydrophilic polymers are another typical design of polymer micelles for drug delivery. A lower critical solution temperature (LCST) and an upper critical solution temperature (UCST), which regulate the polymer solubility with respect to temperature, are characteristics of these polymers. If this polymer is utilized to create a stably dispersed polymer micellar shell below the LCST, the medication enclosed by polymer micelles can be promptly released from the micellar core once the temperature surpasses the LCST (for example, when administered or transferred to a high-temperature location). Because of this temperature response property, polymer micelles with LCST properties can be used as carriers for therapeutic drugs combined with topical hyperthermia.

Compared with other nanocarriers, polymer micelles have better mechanical strength and drug carrying capacity, and have broad application prospects in the biomedical field. This research briefly introduces the properties of polymer micelles, summarizes the mechanism of polymer micelles in detail, and systematically summarizes their applications in biomedical fields such as drug sustained release, medical imaging, cancer immunity, and vaccine design. In addition, based on the current problems and application prospects of polymer micelles, some problems and application prospects of polymer micelles are summarized and prospected, which provides a reference for the further development and application of this nanomaterial.

2. Applications of polymer micelles

2.1. Application of polymer micelles in drug delivery

Polymer micelles composed of block copolymers with amphiphilic properties are nanoscale drug delivery systems, which has shown great advantages in the disease treatment. Because of the great difference in solubility between hydrophilic and hydrophobic segments, amphiphilic block

copolymers can form a core-shell structure with a range of microscopic size by self-assembly in aqueous environment. In diluted solvent, the amphiphilic micelles, which function as surfactants, can lessen the surface force at the interface between air and water. The more amphiphilic blocks in the solvents, the higher the absorption formed at the interface until a core-shell structure is formed—the hydrophobic segment is separated in the solvent whereas the hydrophilic segment surround the core. At this point, critical micellar concentration (CMC) is reached [7]. A range of pharmaceuticals with varied properties, including tiny molecules chemical medications, genes, and proteins, can be contained in the polymer micelle due to the designed structure of the core component of the block copolymer that makes up the polymer micelle. This depends on the synthesis process and the properties of the drug release, as shown in Figure 1. According to the properties of the polymers and the drug, a range of preparation methods are available, including dissolution, solvent evaporation, and film water legalization.

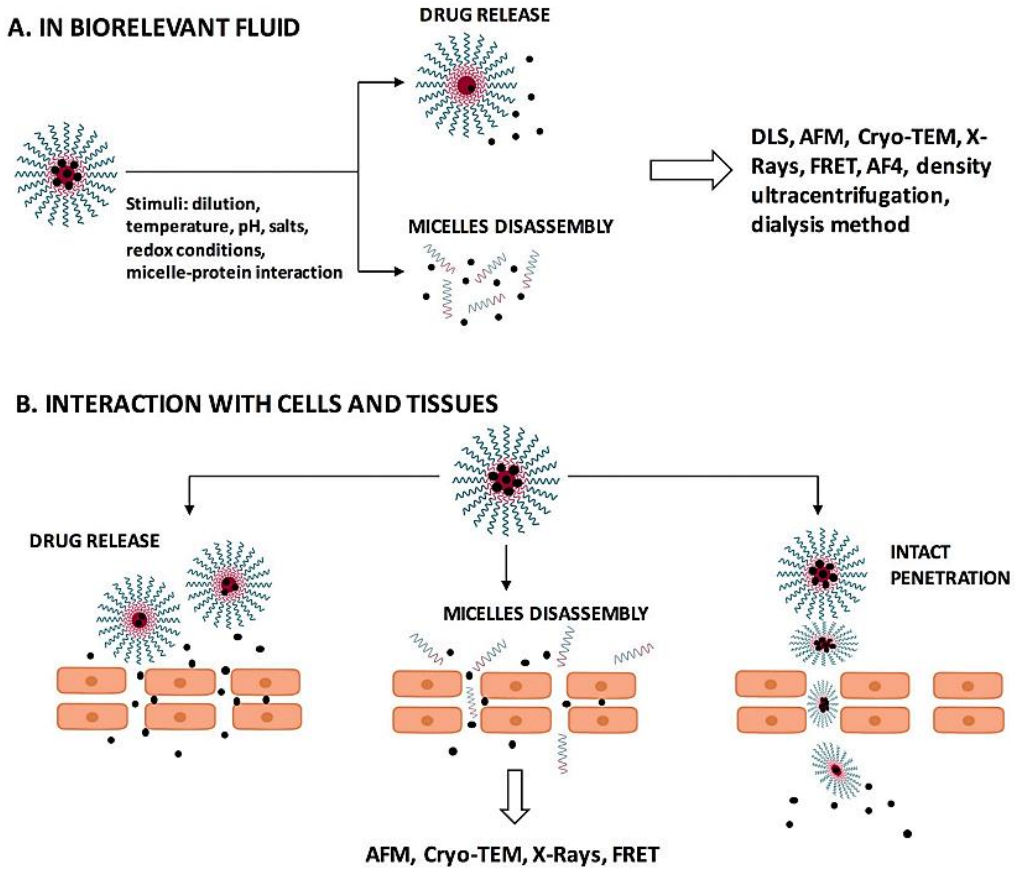

Figure 1. Schematic illustration of drug release and micelle interactions with cells and tissues [7]

The release of drug will happen when the polymeric micelles disassembling. In order to keep the drug release under control, the good thermochemical as well as kinetic stability is indispensable. In addition, the stimuli-responsive polymeric micelles are worth further researching, for that these micelles can model the release of drugs by the response of various stimulus, including pH, ultrasound and temperature.

The use of polymer micelles to deliver therapeutic small-molecule pharmaceuticals offers numerous benefits over the more conventional free small-molecule drug treatment. First, the hydrophilic shell can turn the polymer into gelatin if the polymer micelles contain hydrophilic block polymers. Without being seen and removed by the RES, the bundle spends a lot of time circulating in the blood. However, they are also stable in physiological settings and biological fluids. Additionally, because these polymers are difficult to breakdown, encapsulating small-molecule medications in the center of micelles can extend their shelf lives. Second, after being enclosed in

polymer micelles, small-molecule medicines often have bigger particle sizes that are large enough to avoid renal excretion (15 – 30 nm) while typically having an acceptable size to promote drug extravasation and accumulation at tumor locations. Last but not least, hydrophobic small molecule medications may be quickly and simply mixed into polymeric micelles.

2.2. Application of polymeric micelles in gene delivery

Antitumor drugs mainly include chemotherapy and nucleic acid. However, chemotherapy drugs are highly toxic to normal cells and need to reach the target cells to perform their functions. Current research in tumor research focuses on understanding and targeting genetic changes in cancer cells. For example, small interfering RNA (siRNA) and DNA. The siRNA is a useful therapeutic tool for knocking out genes that directly or indirectly contribute to abnormal proliferation to abnormal proliferation of cancer cells. As nucleic acid drugs are low in endocytosis and easily degraded, the efficiency of gene delivery seriously hinders the clinical translation of antitumor drugs.

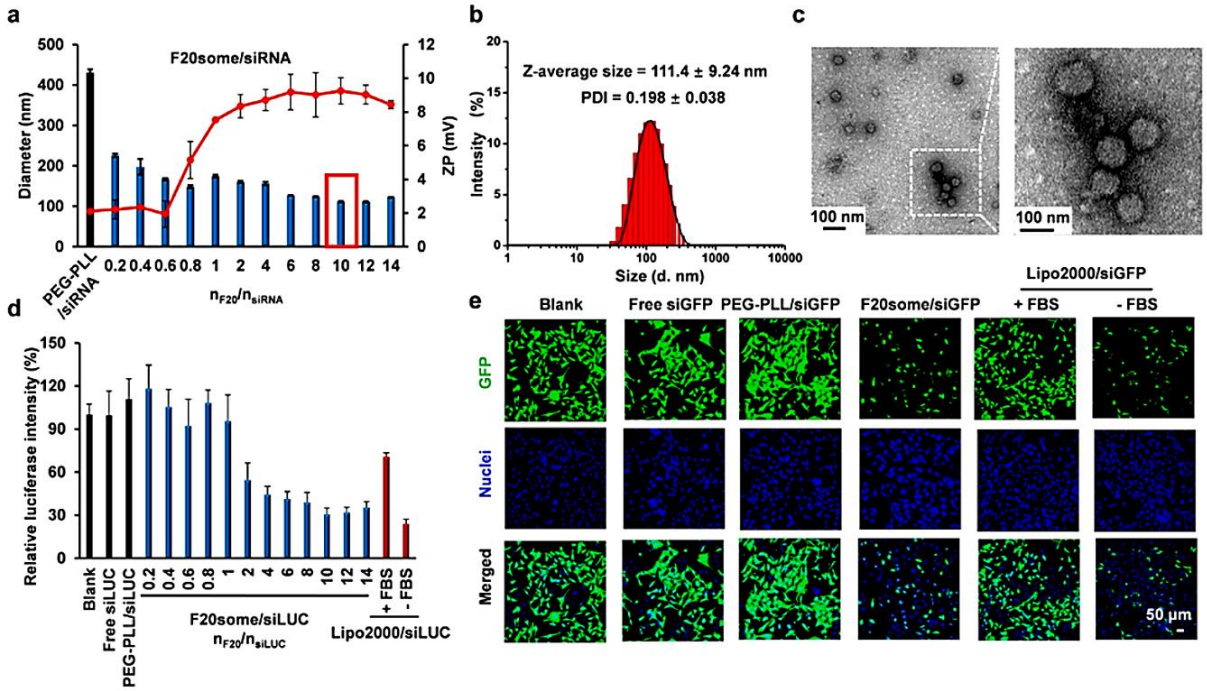

Figure 2. Results analysis of *in vitro* delivery using siRNA [8]

One of the main problems of nucleic acid delivery is their physicochemical properties. They are hydrophilic, negatively charged, and have a high molecular weight, which makes it impossible for them to pass through the cell’s lipid membrane. In addition, if nucleic acid drugs enter through endocytosis, they may be rapidly degraded and cannot pass through the nuclear membrane. However, amphiphilic block copolymers may self-assemble to form polymer micelles, which can be used for gene transfer. Notably, due to their smaller size, polymer micelles are often more stable than other molecules (such as complex of polymer-nucleic acid), which makes them a better substitute for nucleic acid delivery. Thus, encapsulation usually provides far greater protection for genes that must remain stable against serum degradation than chemical alteration. Polyplex nanovesicles created by PEG-PLL and monocateral oligonucleotides were discovered by Shen’s group to be a very efficient delivery platform for siRNA and cytosolic protein [8], as shown in Figure 2. Additionally, the given continues to be very effective. Also, in vivo, SiBCL-2 is effectively delivered via F20 body nanovesicles, which also have synergistic anticancer effects. This method is very versatile and adaptable to different mono-strand oligonucleotides, making it possible to distribute various functional oligonucleotides.

2.3. Application of polymer micelles in tumor imaging

The imaging of tumor tissue technology is of great significance for the detection and diagnosis of the disease and the distribution of tumors. It can also help guide the clinicians to formulate reasonable treatment plans. Currently, near-infrared fluorescence (NIR), computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) have a wide range of application in clinical diagnosis, assessment and treatment. The modifiable polymer micelles allow MRI contrast agents or fluorescent dyes to be modified into the polymer micelles for imaging.

Optical imaging has great advantages in terms of both practicality and cost, making it a diverse and basic medical tool for cancer and tumor imaging. Comparing to other nanocarriers, the polymeric micelles have high stability, biocompatibility, and changing the shape of the polymeric micelles in order to targeting drug delivery. As shown in Figure 3, the most popular imaging technique in biological research is optical imaging with fluorophores because it is simple to label, has a large dye library that is accessible, allows for multi-channel imaging, has a high sensitivity, and can be utilized in real-time [9]. A variety of fluorescent transducers have shown potential for selective tumour imaging. However, because the dye will be distributed throughout the body and some tissues have high levels of autofluorescence, it is difficult to visualize tumors after systemic administration using fluorescence imaging. Polymeric micelles are ideal supramolecular matrices that can stably confine small molecule probes inside nanoparticles. Gu's group [10] proposed a method to construct H_2S-specific nanoprobes by capturing small-molecule probes in the hydrophobic core of surface-crosslinked micelles (SCMs), improving stability and sensitivity of the probes. In order to integrate tiny fluorophores with functional building groups, which can increase the stability of fluorophores or improve the water solubility of nanofluorescent probes, amphiphilic molecules must self-assemble into higher-order supramolecular aggregates.

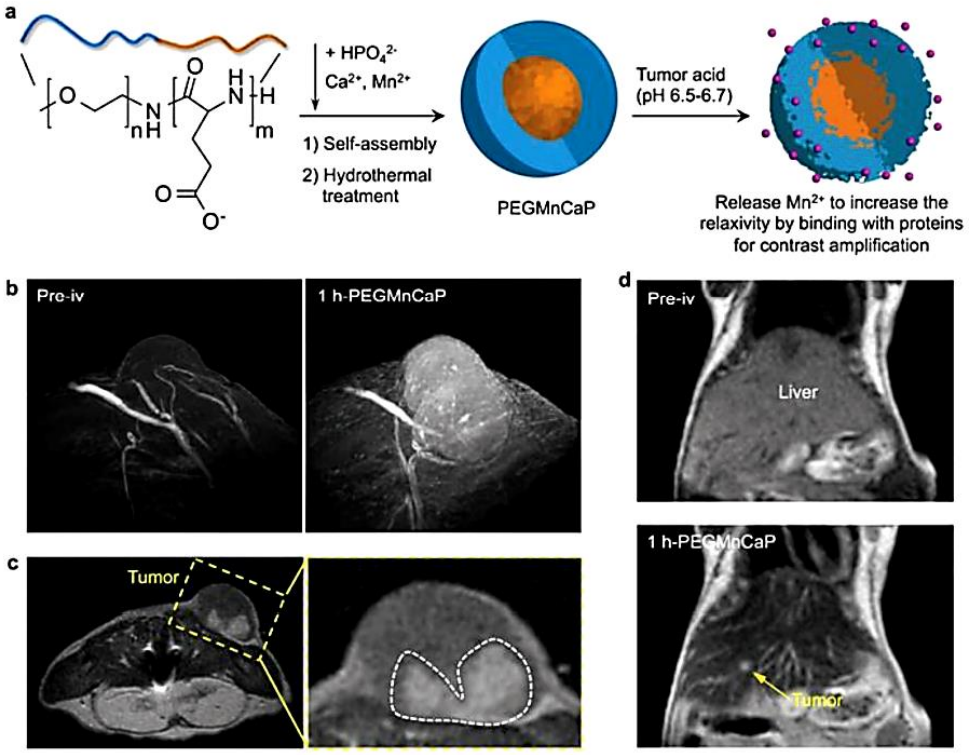

Figure 3. pH-responsive polymer nanomaterials for imaging analysis of tumor malignancies [9]

Polymer nanocomponents loaded with fluorescent probes were used to accurately image tumours. The diffusion of assemblies into other organs like the liver, kidney, or spleen restricts the precision of systematic fluorescence imaging, but the selective tumor accumulation based on these methods makes tumor plainly visible.

2.4. Application of polymeric micelles in cancer immunotherapy

Traditional cancer treatment aims to destroy cancer cells directly, while cancer immunotherapy aims to use patients' own population of immune cells to recognize and kill cancer cells. Our immune system's immune cells, such as effector T cells, regulatory T cells (Treg), dendritic cells (DCs), natural killer cells (NK), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs), play a critical role in initiating and enhancing specific anti-tumor immune responses. Multiple strategies have been developed to stimulate anti-tumor immunity specifically against cancer cells, including cancer vaccines, antibodies and immunostimulatory adjuvants. These strategies work to enhance the suppressive TME as well as existing anti-tumor immunity.

2.5. Application of polymer micelles in vaccine design

Nanotechnology-based multifunctional nanovaccine has several advantages over traditional vaccine formulations. First, nanovaccine can co-deliver antigen and adjuvant. Furthermore, nanovaccine based on environmental stimuli not only maintains the structural integrity of the vaccine in serum, but can also be selectively triggered by specific stimuli in the environment to promote specific payload release. In addition, in addition to ensuring the normal delivery and release of antigens and adjuvants, nanovaccine can also solve off-target problems and improve safety and efficiency. More importantly, vaccines play an important role in tumor immunotherapy. The tumor microenvironment (TME) is a significant and complex target of tumor immunotherapy, which helps tumor cells invade and inhibits the activation of T cells [11], as shown in Figure 4. The use of specialized nanovaccines can reverse the tumor microenvironment, thereby increasing T cell infiltration.

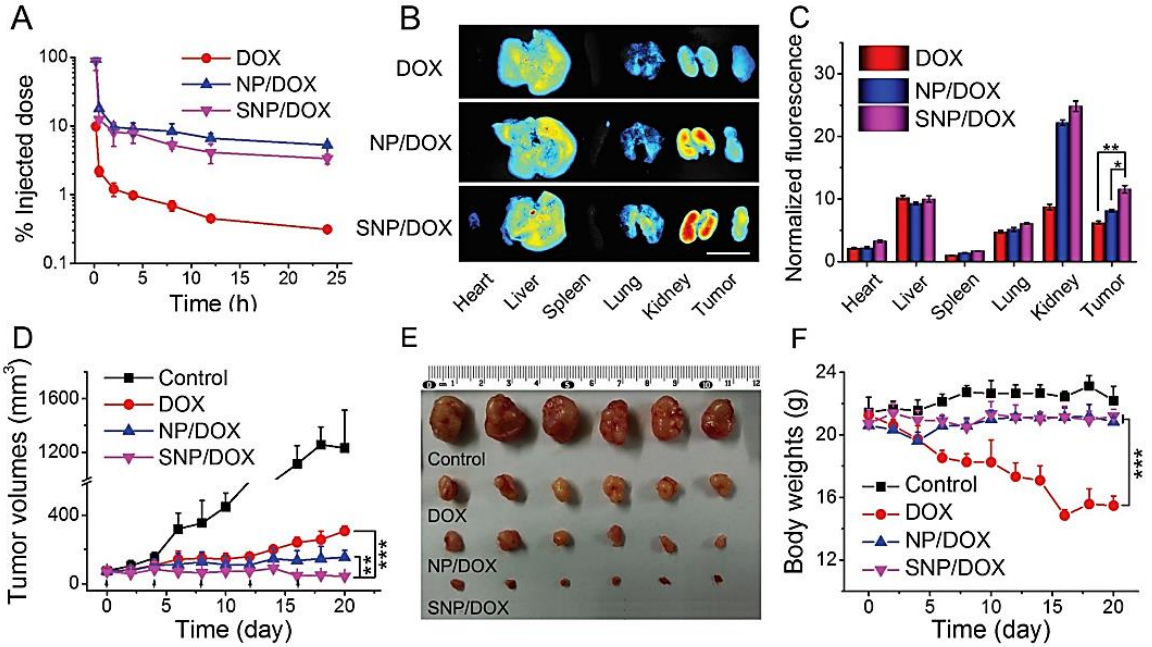

Figure 4. The pharmacokinetics, biodistribution and antitumor efficiency analysis of the prepared materials in a mouse model of lung cancer xenografts [11]

3. Conclusions

Polymer micelles, based on its nanostructure, have been applied in biomedical fields such as drug sustained release, medical imaging, cancer immunity, and vaccine design. However, even though having gain some knowledge of polymer micelles, the application of polymer micelles in the pharmaceutical field still faces many challenges, such as the potential toxicity of polymer micelles, the potential mechanism between the stability of micelles and drug delivery is not fully understood,

how micelles interact with drugs to affect the stability of drugs, and the relationship between drug release and micelles. Nevertheless, one of the main problems faced by polymer micelles in medicinal use is the scalability of their production. Micelles with high dosing and good stability can be prepared in the laboratory, but in large-scale production, variables have different effects on physical factors, which can lead to the inability to replicate micelles with the same quality properties and specifications. Also, the high cost of mass production cannot fully meet the requirements. Researchers need to conduct in-depth research on the different properties of polymer micelles, and thoroughly understand the biological distribution, pharmacokinetics, safety characteristics, immunogenicity, immunoreactivity and degradation in vivo of polymer micelles, so as to achieve large-scale application of polymer micelles.

References

[1] Manjappa A S, Kumbhar P S, Patil A B, et al. Polymeric Mixed Micelles: Improving the Anticancer Efficacy of Single-Copolymer Micelles [J]. Critical Reviews in Therapeutic Drug Carrier Systems, 2019, 36(1): 1-57.

[2] Cabral H, Miyata K, Osada K, et al. Block Copolymer Micelles in Nanomedicine Applications [J]. Chemical Reviews, 2018, 118(14): 6844-92.

[3] Kakizawa Y, Kataoka K. Block copolymer micelles for delivery of gene and related compounds [J]. Advanced Drug Delivery Reviews, 2002, 54(2): 203-22.

[4] Xiao K, Li Y, Luo J, et al. The effect of surface charge on in vivo biodistribution of PEG-oligocholic acid based micellar nanoparticles [J]. Biomaterials, 2011, 32(13): 3435-46.

[5] Velluto D, Demurtas D, hubbell J A. PEG-b-PPS diblock copolymer aggregates for hydrophobic drug solubilization and release: Cyclosporin A as an example [J]. Molecular Pharmaceutics, 2008, 5(4): 632-42.

[6] Shi Y, Lammers T, Storm G, et al. Physico-Chemical Strategies to Enhance Stability and Drug Retention of Polymeric Micelles for Tumor-Targeted Drug Delivery [J]. Macromolecular Bioscience, 2017, 17(1).

[7] Ghezzi M, Pescina S, Padula C, et al. Polymeric micelles in drug delivery: An insight of the techniques for their characterization and assessment in biorelevant conditions [J]. Journal of Controlled Release, 2021, 332: 312-36.

[8] Zhou Q, Xiang J, Hao L, et al. Polyplex nanovesicles of single strand oligonucleotides for efficient cytosolic delivery of biomacromolecules [J]. Nano Today, 2021, 39: 101221.

[9] Mi P, Wang F, Nishiyama N, et al. Molecular Cancer Imaging with Polymeric Nanoassemblies: From Tumor Detection to Theranostics [J]. Macromolecular Bioscience, 2017, 17(1): 1600305.

[10] Liu H, Xu G, Zhu T, et al. Rational design of water-dispersible and biocompatible nanoprobes with H2S-triggered NIR emission for cancer cell imaging [J]. Journal of Materials Chemistry B, 2020, 8(28): 6013-6.

[11] Chen J, Ding J, Wang Y, et al. Sequentially Responsive Shell-Stacked Nanoparticles for Deep Penetration into Solid Tumors [J]. Advanced Materials, 2017, 29(32): 1701170.