Applications of Polymeric Micelles for Drug Delivery

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Abstract. Polymeric micelles have attracted more and more attention in the biomedical field due to their controlled synthesis and sustained drug release, where a diverse of different drug carriers based on the polymeric micelles have been developed in recent years. This research will analyze the application and development of polymeric micelles that derived from block copolymers in biomedicine. There are three processes in drug delivery of drug carriers prepared by polymeric micelles, including micellar drug loading, micellar drug release and targeted therapy. In the polymeric micelles system, the reason why the solubilization and stabilization of drugs are improved is that the hydrophobic interaction and forming of hydrogen bond between micelles-system and drugs. This research also gives basic mechanism for polymeric micelles for passive and active drug targeting. What makes micelles ideal hosts for hydrophobic anti-cancer drugs or other targeted drugs is the hydrophobic nature of its core. This can make the drug more stable. In addition, this research is written to cover the latest information on polymeric micelles and methods of synthesis for applications. The advantages and disadvantages of its use as a drug carrier are also included. And it highlights the conditions that polymeric micelles need to meet as specific delivery tools in various targeting situations.

Keywords: Polymeric Micelles, Drug Carriers, Biomedicine.

1. Introduction

To date, thousands of people around the world are still dying of cancer. For example, the National Cancer Centre released the latest edition of national cancer statistics: 2.414 million people died of cancer in China in 2016 [1]. To this end, a diverse of different countries are trying hard investing a lot of research in cancer diagnosis and treatment, and various cancer treatment methods have also been developed [2]. Several attempts such as surgery, radiation therapy and systemic therapy treatment have been made to improve cancer survival rates and life patients have after the cancer treatment. In the physicochemical field, polymer-based nano-system has emerged as great platforms for drug delivery in treatment processes for different needs. For decades, nanomedicines like polymeric micelles are gradually being applied in conventional therapies for cancer application. The challenge of overcoming metastatic cancer is further addressed through a combination of nanotechnology and cancer diagnosis.

Generally, when there is a change in physicochemical properties in aqueous solution, micelles are formed, where the formed micelles contain a hydrophobic core on the inside and a hydrophilic shell on the outside. Compared with traditional surfactant-based monomer micelles, polymer micelles possess covalent bonds between various surfactant molecules in the hydrophobic core. For the formation of polymer micelles, the critical micelle concentration (CMC) plays an important role in polymeric micelles formation. For example, when copolymer concentrations above CMC, the self-assembly of amphiphilic polymers can lead to the formation of different types of polymeric micelles, such as polymeric nanoparticles. In addition, the value of the CMC is also one of the most essential metrics for determining the thermodynamic stability of micelles. Surface tension measurement, conductivity and light scattering techniques can be used to analyze the CMC of polymers. Polymeric micelles are characterized by having a lower CMC index. As a result, polymeric micelles have just the right kinetic stability compared with surfactant micelles with low molecular weight. For instance, these low-molecular-weight surfactant micelles can disintegrate within microseconds. However, in polymeric micelles, the drug can form polymer-drug conjugates with it. This gives polymeric micelles a better ability to transport drugs.

Nanocarriers are widely used in drug delivery systems due to their small size effect. At present, several generations of nanoparticles-based delivery technologies used for drug targeted transportation include passive nanoparticles, active nanoparticles and multifunctional nanoparticles [3]. Each generation shows higher efficiency and selectivity. Based on the excellent performance of nanocarriers for drug delivery, polymeric micelles can also be used to prepare different nanocarriers, such as polymeric microparticles (PMs). Thanks to the discovery of stimulus responsive polymers, a new generation of more effective PMs can be prepared by using different preparation strategies. The unique core-shell construction of PMs confers several advantages. The benefits of PMs over other nano-systems, particularly lipid-based nanoparticles, lie in their tiny size and the existence of a micelle corona. Micelles benefit from these features because they manage their surface chemical properties such as surface wettability, all of which contribute to their steric stability. Because of its small size, the PMs loaded with drugs is absorbed by intestinal mucosa, and then delivered to the treatment target through the circulatory system. the prepared different PMs have the prolonged half-life because macrophage phagocytic processes misidentify them, and have the potential to enhance the pharmacokinetics of capsule drugs, which are advantageous because they can transport a great deal of medicine, are simple to produce in large quantities at a low cost and can transport a great deal of medicine. In addition, PMs have simple preparation, low price and high drug loading. After delivering the target drug to its therapeutic target via circulation, PMs deliver the medication to its therapeutic goal via circulation. Therefore, this research mainly introduces the methods of polymeric micelles loading drugs, drug release regulation strategies and their applications in disease treatment.

2. Applications of polymeric micelles for drug delivery

By definition, a polymer micelle is a copolymer that can self-assemble. It can be either a diblock or triblock. A characteristic feature of polymer micelles is that they are usually sphere-shaped structures with a core-shell. However, under certain conditions, micelles such as snail-shaped micelles can also exist. The core of a polymer micelle is a hydrophobic structure, and the shell is hydrophilic. As a result, polymeric micelles have been widely used in a diverse of various filed, such as food safety, functional material synthesis and energy chemicals. This is a prerequisite for such micelles to be promising drug carriers. During drug transport, the drug is stored in the core. In a liquid environment, the outer shell of the micelles spontaneously creates a steric barrier effect to ensure solubility and effective drug release, thus preventing the micelles from clumping together during drug delivery.

Adaptability is also a prominent feature of polymeric micelle core-shell structures as drug transport vehicles. For example, of the many hydrophilic blocks, poly(ethylene oxide) (PEO) is widely used. Its monomeric subunit consists of -CH2-CH-O. For the end groups, there are correspondingly different options because of the manufacturing technology. Hydroxyl or methoxy are the usual choices. Reactive end groups, such as amines, are added to molecular vectors in situations where it is predicted that the vectors may undergo conjugation. PEG blocks prevent micelles from being opsonized, which in turn reduces the number of reticuloendothelial system (RES) cells that recognize micelles. This results in an increase in plasma residence time, which in turn makes it possible to target tumors passively through increased permeability and retention (EPR) effects. It is necessary for micelles to include components that are either biodegradable or that are eliminated by the kidneys in order to prevent micelle or build-up in the body.

The selection of the hydrophobic block is highly impacted by the stability of the micelle in terms of both thermodynamics and kinetics. The pace at which hydrophobic blocks in micelle cores disassemble is a primary factor in determining kinetic stability. Interactions between molecules are what determines the thermodynamic stability of a system. Drug transporters based on polymeric micelles is now under consideration, and many hydrophobic blocks have been proposed. Phospholipids and long-chain fatty acids, poly(glycolic) acid, and poly(aspartic) acid are examples of these.

2.1. Drug loading methods

Different drug loading methods based on polymer micelles are introduced in this section. For example, common drug loading methods based on polymer micelles include dialysis method, oil-in-water emulsion solvent evaporation, solid dispersion and freeze-drying method. For the dialysis method, the block copolymer and drug are dissolved in an organic solvent miscible with water, and then the solution is subjected to water dialysis. This is the method that is used for the dialysis procedure. This process is driven by the development of the core. Structures that are erected for the purpose of snaring drug dealers. Because of a semipermeable barrier that permits for the discharge of unloaded and free drug, the polymeric micelles are kept inside the dialysis bag where they are safely controlled. It is possible that this technology, which has been put to substantial use in the lab for the development of polymeric micellar formulations, but it is not scalable enough for application in industrial settings. Another disadvantage of the sort of inclusion in question is that the free drug that is released from the polymeric micellar formulation cannot be properly removed.

As shown in Figure 1, amphiphilic block copolymers can be used to form polymer micelles through self-assembly strategy [4]. The prepared micelles exhibit excellent physical and chemical properties, such as biocompatibility and recyclability, and are widely used to load different drugs to achieve targeted cancer treatment. However, when polymer micelles enter the organism, they may be damaged due to adsorption of proteins in the organism, which may lead to drug leakage before reaching the target site, thus affecting the treatment effect of diseases. Therefore, before drug loading, various factors affecting the stability of polymer micelles (such as CMC and polymeric micelles-drug interaction) need to be considered from the perspective of thermodynamics and kinetics, so as to achieve the drug payload and achieve the best therapeutic effect. In addition, In addition, some effective strategies can be used to improve the stability of micelles to increase the interaction between polymetric micelles and drugs, including chemical conjugation and ionic interaction.

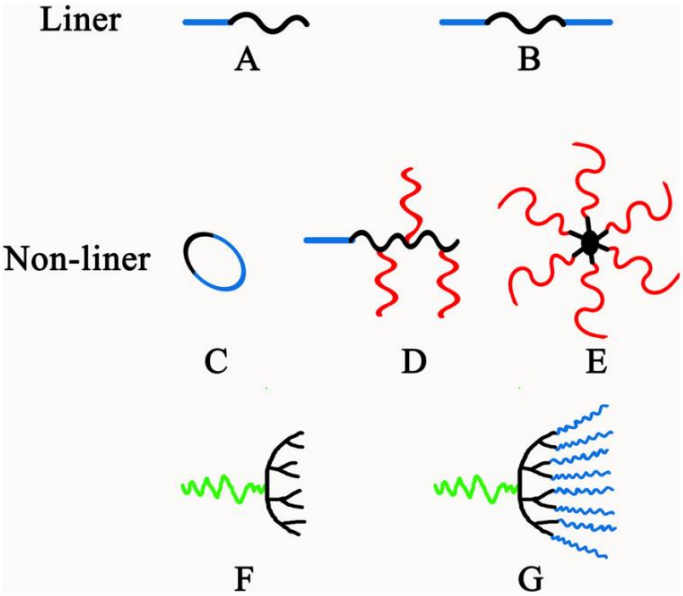

Figure 1. Schematic diagram of polymer micelle formation based on amphiphilic blocks [4].

2.2. Drug releasing

The drug can be loaded via either chemical conjugation or physical encapsulation. However, the drug release mechanisms will differ depending on which method is employed [5]. Medicines that are physically entrapped are released primarily through the process of diffusion, whereas drugs that are chemically linked are released through decomposition or surface erosion of polymers. In addition to the partition coefficient, other key elements that go into determining drug release include drug loading, polymer length and degree of intranuclear crosslinking of micelles. Both on the inside and the outside of the core are viable locations for cross-linking to take place. The consistency of the material in the

center of PMs that can range from solid to glassy to liquid is what establishes their properties. The liquid on the inside causes the drug to gently but steadily leak out of the glassy outside of the container. Micelles will change their conformation in an environment with a low pH, which will allow PEG channels to develop via which the drug may be administered. These properties may be fine-tuned by adjusting not only the content of the polymer mix but also ambient parameters such as pH.

The drug release of polymeric micelles under different pH conditions can be used as an effective drug delivery system to achieve the treatment of different diseases. The preparation of pH responsive polymeric micelles can be realized by forming a core unit with reversible protonation deprotonation or a pH sensitive polymeric micelle between drugs and micelles, and can be used to realize the controlled release of drugs. The combination of pH responsive polymeric micelles and targeting strategies for disease treatment is of great significance for enhancing tumor targeting therapy. The use of pH responsive polymeric micelles not only promotes the controlled delivery of the target drug, but also reduces the side effects of the drug, thereby improving the therapeutic effect, and also provides a new drug delivery system for the treatment of diseases. For example, Son et al. synthesized a pH responsive amphiphilic polyether micelle and used it to design a new intelligent drug delivery system, which showed excellent stability [6]. As shown in Figure 2, they studied the stability of the prepared polymer micelles under different pH conditions. The results show that the prepared micelle is stable at pH=7.4. And the release kinetics data of the drug shows that the release process was controllable.

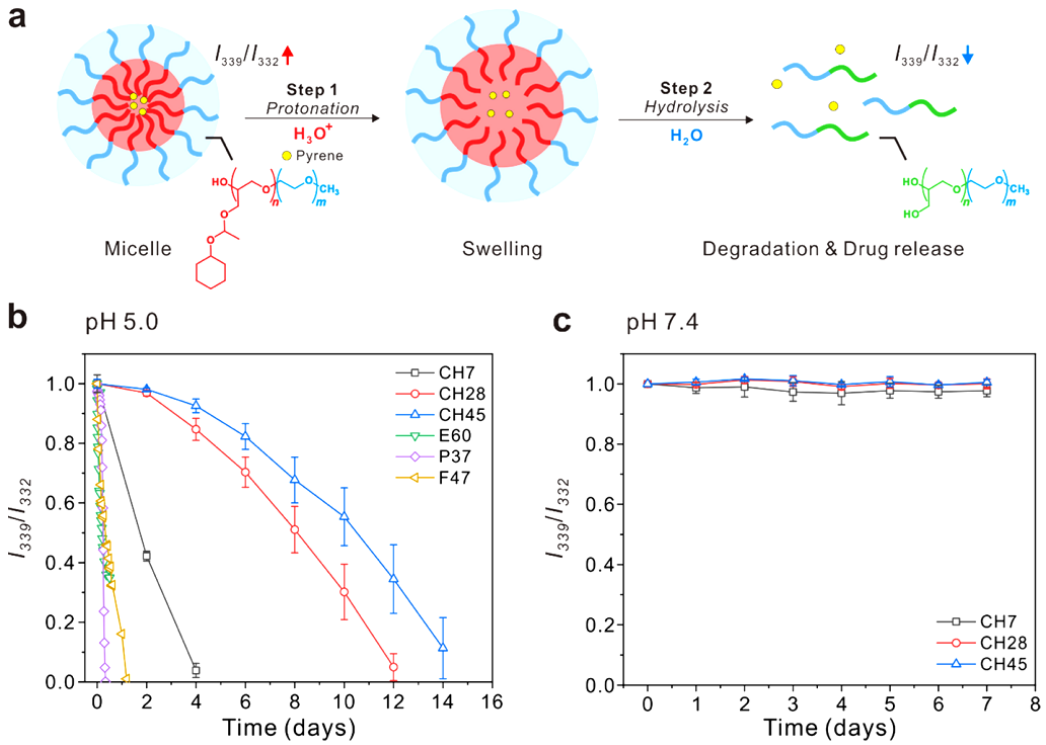

Figure 2. Schematic diagram of drug release curve and corresponding chemical changes, and drug release kinetics of loaded micelles under different pH conditions [6].

2.3. Drug targeting

When delivered through the intravenous route, the increased permeability and retention effect is primarily responsible for the successful passive targeting of polymeric micelles. Most aberrant tumour tissues are characterised by distinctive pathophysiological circumstances. One of them is widespread angiogenesis. As a result of the excessive production of VEGF, it can result in hyper-vascularization and poor lymphatic drainage. These characteristics are in response to the growth of the tumour. This causes the tumours to become leaky and exposes them to the possibility of being penetrated by particles. The effective pore size of most tumours spans from 200 to 600 nm, which

enables the increased penetration of nanoparticles that are in the lower size ranges. Additionally, because tumours do not have a lymphatic system that is highly established, the particles can be maintained preferentially inside the tumour's interstitial for extended periods of time. This EPR phenomenon can be used to one's advantage by nanocarriers carrying pharmaceuticals. Their breakdown makes it possible for the free drug to be released either before or after it is taken up by the cells, leading to a preferential accumulation of the drug in the tissue of the tumour. It should come as no surprise that the size of the polymeric micelles plays a significant impact in this regard.

If drugs are encapsulated in the prepared polymeric micelles, the targeting of drug delivery systems can be effectively improved by precise regulation of the micelles [7]. Chauhan et al. synthesized a silica coated mixed polymer micelle loaded with pidavastatin [8]. In this work, the use of silica can be used to increase the stability of polymeric micelles and achieve controlled drug release. As shown in Figure 3, the prepared polymeric micelles can easily pass through BBB cells without causing any damage, and then reach the target position, showing good targeting.

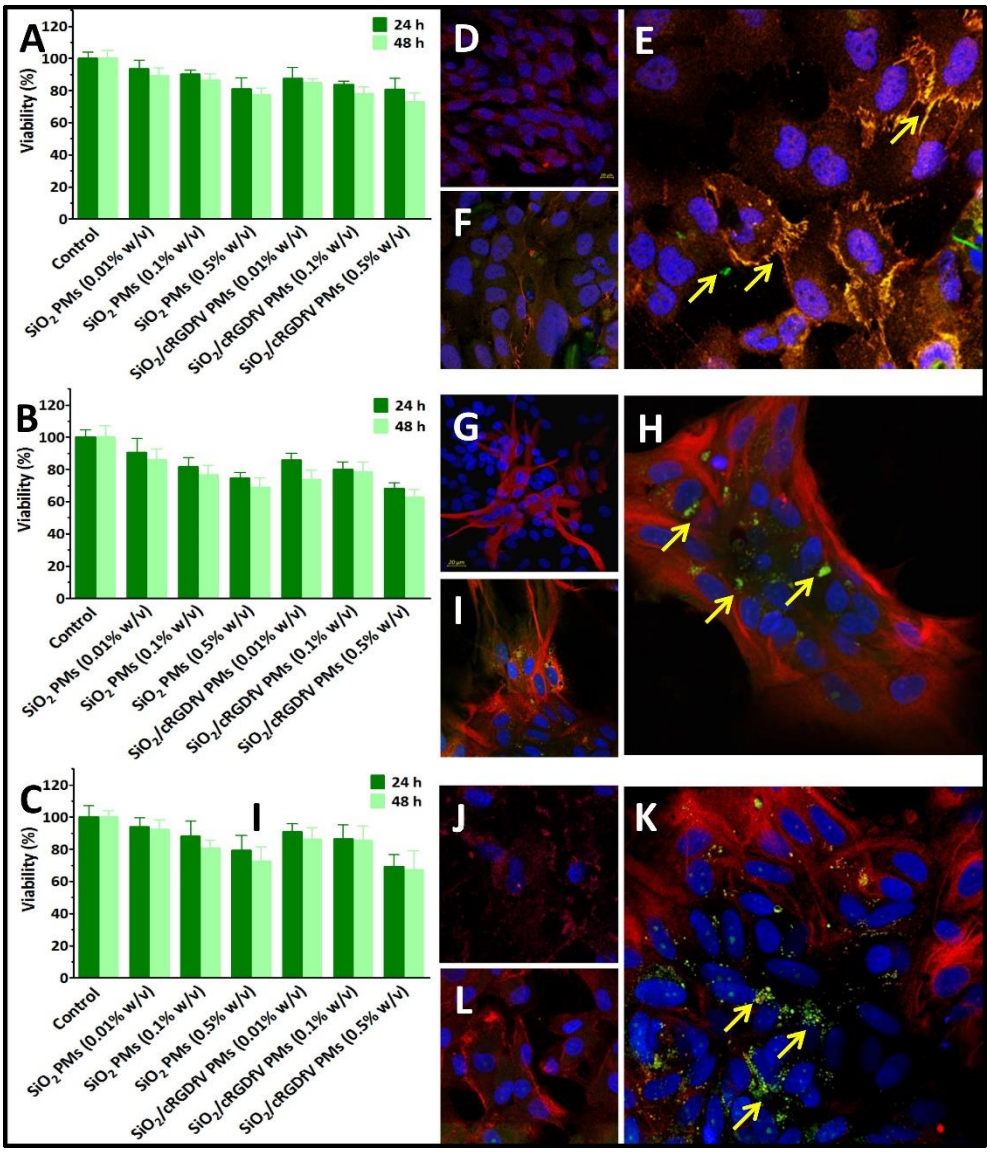

Figure 3. Cell compatibility analysis of the prepared micelles [8].

For this reason, polymeric micelles have been widely used as a drug carrier and have been used to build different functional drug delivery systems to achieve the treatment of different diseases [9]. For example, Barve et al. prepared an enzyme responsive polymer micelle and used it for targeted therapy of prostate cancer, as shown in Figure 4 [10]. The micelles showed very low CMC, high drug loading

and high encapsulation efficiency, and the results show that the polymeric micelle based on enzyme reaction is an effective and promising drug delivery system.

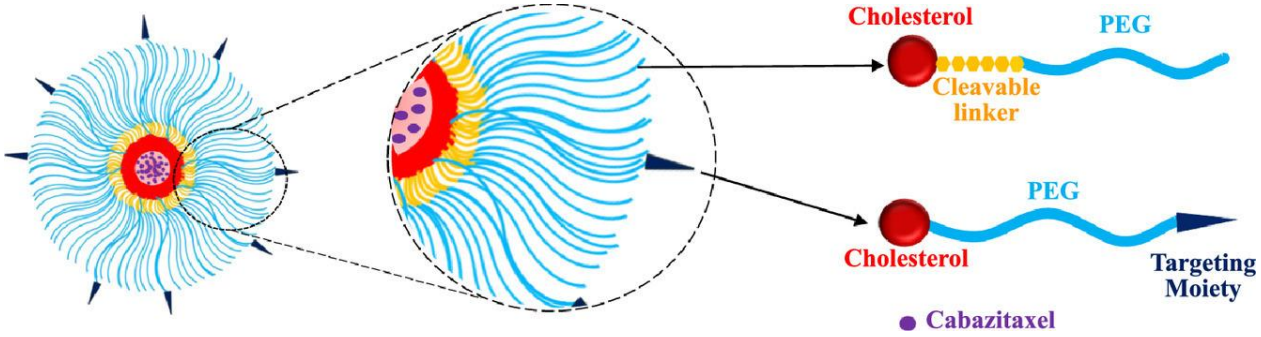

Figure 4. Schematic diagram of drug release curve and corresponding chemical changes, and drug release kinetics of loaded micelles under different pH conditions [10].

3. Conclusions

In summary, it has been demonstrated that polymeric micelles are the most effective alternative drug carriers. The incorporation of noticeably greater quantities of pharmaceuticals, an increase in the amount of time spent circulating in the blood, and thermodynamic stability are some of the benefits that may be gained from employing mixed polymeric micelles. It's possible that the polymeric micelle's core may be optimized for drug loading in order to lengthen the useful lifetime of the micelle. Both chemical conjugation and physical entrapment are viable options for the encapsulation of insoluble medicines within the micellar core. Chemical conjugation is one method, while physical entrapment is another. For the purpose of drug integration, it has been demonstrated that the use of physical procedures is preferable to the application of chemical approaches. To get started with the passive drug targeting strategy, it may begin by either including a temperature- or pH-sensitive polymer probes. Both of these strategies are viable options. In spite of this, only a select few polymeric micellar formulations have been shown to be effective in the targeted administration of medications inside of a biological system. Previous attempts to construct micelle-forming drug conjugates have, for the most part, been unsuccessful. This is mostly due to the fact that the generated micelles are too stable to experience substantial drug release at the sick region. Polymeric micellar nanocontainers and polyion complex micelles both have the potential to leak their drug contents before the period that was originally planned for their release. In general, the problem that must be overcome is that drug carriers can effectively release drugs in biological systems and are not affected by the internal environment of organisms.

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