Application of Different Stimuli-Responsive Polymeric Micelles for Drug Release

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Abstract. Achieving controlled release of drugs in disease treatment can greatly improve the utilization rate and therapeutic effect of drugs. Therefore, the development of functional materials with controllable drug release has received more and more attention, such as stimuli-responsive polymeric micelles. The so-called stimuli-responsive polymeric micelles are a new type of polymer micelles that can be used to give responses to different stimulus conditions, such as endogenous stimuli (e.g. light, temperature, ultrasound intensity, magnetic field or electric field) and exogenous stimuli (e.g. redox potential, pH, or enzyme concentration). They can exhibit distinctive size and stability with the variations of the endogenous or exogenous environment. Stimuli-responsive polymeric micelles have several desirable biotechnology applications including their potential use as drug delivery vehicles because tumor tissue and normal tissue is different in physical and chemical properties, where they are very sensitive to endogenous or exogenous environmental changes. This research would mainly discuss different stimuli-responsive polymeric micelles for developing a diverse of drug delivery systems, including light and magnetism response, temperature and ultrasound response, redox response, pH response and enzyme response. Some recent advances and future directions would be briefly referred to as well.

Keywords: Stimuli-Responsive, Cancer Treatment, Polymeric Micelles, Drug Release.

1. Introduction

Polymeric micelles are a kind of high polymer materials that contains amphiphilic core-shell structure, which is formed by the interaction of hydrophilic and hydrophobic chain segments. A wide range of polymeric micelles can self-assemble and form their structure in the suitable solvent. For instant, Yang et al. synthesize amphiphilic hyaluronic acid derivative, which has the capability to turn into nanomicelles in the solution such as aqueous solution [1]. The design and synthesis of polymer micelles can also improve the properties of polymer micelles. For example, Zhang et al. has improved the properties of poly-caprolactone (PCL) and poly-L-lactic acid (PLLA) [2]. PCL could be improved by copolymerization or blending of PCL and PLLA. Polymeric micelles have become one kind desirable vehicles for anticancer drugs nowadays. Compared to traditional medicine, polymeric micelles exhibit plenty of advantages. They have the smaller particle size which enable them to seep out into human body. What's more, they are more stable, and their permeability and retention effect are enhanced. In terms of biological adaptability, polymeric micelles have the capability to fit in the environment of human body, they have almost no toxicity which will reduce the side effects on the human body. To achieve the achievement that to let the drug enable to deliver to the target tumor cells and release adequately, a high-efficiency mean is that to devise some stimuli-responsive polymeric micelles. Stimulus-responsive polymers are a class of macromolecular systems with "intelligent" behavior. They enable to respond to exogenous stimuli and endogenous stimuli.

Light, temperature, ultrasound, electric field and magnetic field belong to exogenous stimuli. And pH, redox, gas and enzymes typically belong to endogenous stimuli. After polymeric micelles receive a kind of stimuli, they can change its macromolecular structure or morphological structure greatly, thus affecting its size and stability. And then they have the ability to manifest the relevant function. Stimulus-response polymers are sensitive to exogenous stimuli and endogenous stimuli. Upon receipt of stimuli, they trigger reversible or irreversible changes in molecular structure, which changes the behavior of the bulk or liquid phase of macromolecular systems. Normally, the morphological structure the polymeric micelles can be spherical, vesicular worm-like and rod-like. To date, the effect

of polymeric micelles' size and structure on delivering the drug to the targeted cell has been extensively studied. Baccile's group critically discuss the use of bio-surfactants, they use bio-surfactants agents to allow the nanoparticles to be more stable on the solvent [3]. These findings can be applied on proteins, polymers, enzymes and polyelectrolytes. Nevertheless, the morphological effects of polymeric micelles are rarely reported. Martin et al. studied the loading and release behavior of salbutamol sulfate with A-lactose monohydrate particles and found that the morphology of particles has an important influence on the distribution, depolymerization and deposition of drugs [4]. The elongated carrier has a better dispersion effect on drugs than the spherical carrier, and is easy to move. The higher the elongation of the carrier, the more conducive to the deposition of drugs, the better the penetration of lung tissue.

In this new era, health care is a significant topic that everyone is concerned about. Among a variety of diseases, cancer is one troublesome disease that makes everyone fear. In other treat cancer, efficient delivery of drugs to tumor cells is a critical point. From the researches in the field of the stimuli-responsive before, the application of polymeric micelles in drug targeted therapy still has a lot of limitations, such as the unstable polymeric micelles in human body and slow drug release. Compared with the traditional drug delivery tactics, the drug delivery system can be able to significantly enhance the solubility and stability of drugs, directly deliver drugs to human tissue lesions, and improve the utilization rate of drugs. The combination of two or more drugs into a multi-drug delivery system can better play the synergistic therapeutic effect between drugs. Polymeric micelles usually are used to delivery drugs to tumor. It can load the medicine and release when reach the place where the tumors are. Compared with normal cells, the excessive proliferation of tumor cells leads to a unique tumor microenvironment, which is characterized by low pH, high reactive oxygen species, high glutathione and high specific enzyme expression and so on. These characteristics precisely provide the foundation for the emergence of stimuli-responsive molecular micelles. The stimuli-responsive polymeric micelle is a successful improvement, some researchers also focus on modifying the chemical reactions that trigger drug release. A great instant is that they put the click chemistry into use. Click chemistry is a cascade of reactions that combine chemistry reaction with rapid mating. For example, the representative reaction of click chemistry is the copper-catalyzed azide–alkyne cycloaddition. The speed of the release of the drug would increase with the help of click chemistry. Therefore, how to combine the click chemistry with polymeric chemistry is an important topic that every researcher can concentrate on.

This research will focus on several kinds of exogenous stimuli and endogenous stimuli, discussing some typical morphological structures of polymeric micelles and their advanced applications. The research would divide the main body contents into two main types of stimuli (exogenous stimuli and endogenous stimuli). Additionally, this research would discuss some normal reactions of each kind of stimuli and their respective prospects.

2. Exogenous stimuli-based polymeric micelles

2.1. Light and magnetism response

Light is one of the most significant stimuli among the many kinds of stimuli in drug delivery applications because of its non-invasive character, remote operation with great ease, and high spatial and temporal resolution. Light-responsive polymer micelles are typically obtained by incorporating or binding of chromophores into polymer structures, such as azobenzyl, pyrene, cinnamyl, spirobenzopyrane, or nitrobenzyl and so on. Under light conditions, the nanostructure of the polymer micelles would change, and then the micelles open out, thus drugs which in the polymeric micelles would release. Light-responsive polymeric micelles allow precise control of the wavelength and intensity of a site-specific payload to be released at the desired disease site. For instant, Lee et al. develop a kind of light-responsive polymeric micelles named poly-(ethylene glycol)-block-poly-l-lysine (PEG-PLL), which is grafted by DNQ group [5]. And this kind of polymeric micelles is called PEG-PLL-DNQ and has high stability and is developed by π-π stacking interaction. The ratio of

intensity in 373 nm to the intensity in 383nm is called polarity parameter. This value is close to 1 when polymeric micelles are in hydrophobic environments. In hydrophilic environments, this value increase to close to 2. Under this circumstance, the researchers are able to know that pyrene is in the inlayer of the polymeric micelles. The pyrene encapsulate in DNQ and the ratio value of intensity in 373 nm to the intensity in 383 nm would change at different concentrations of PEG-PLL-DNQ a 37°C. At high concentrations, the value would reach a plateau. The process light-responsive polymeric micelles can divide it into two-photon processes and one-photon process. Compared with two-photon processes, the polymeric micelles with single-photon absorption show more ideal wavelengths and are more effective. In addition, the prepared polymeric micelles also have low toxicity and good stability (Figure 1).

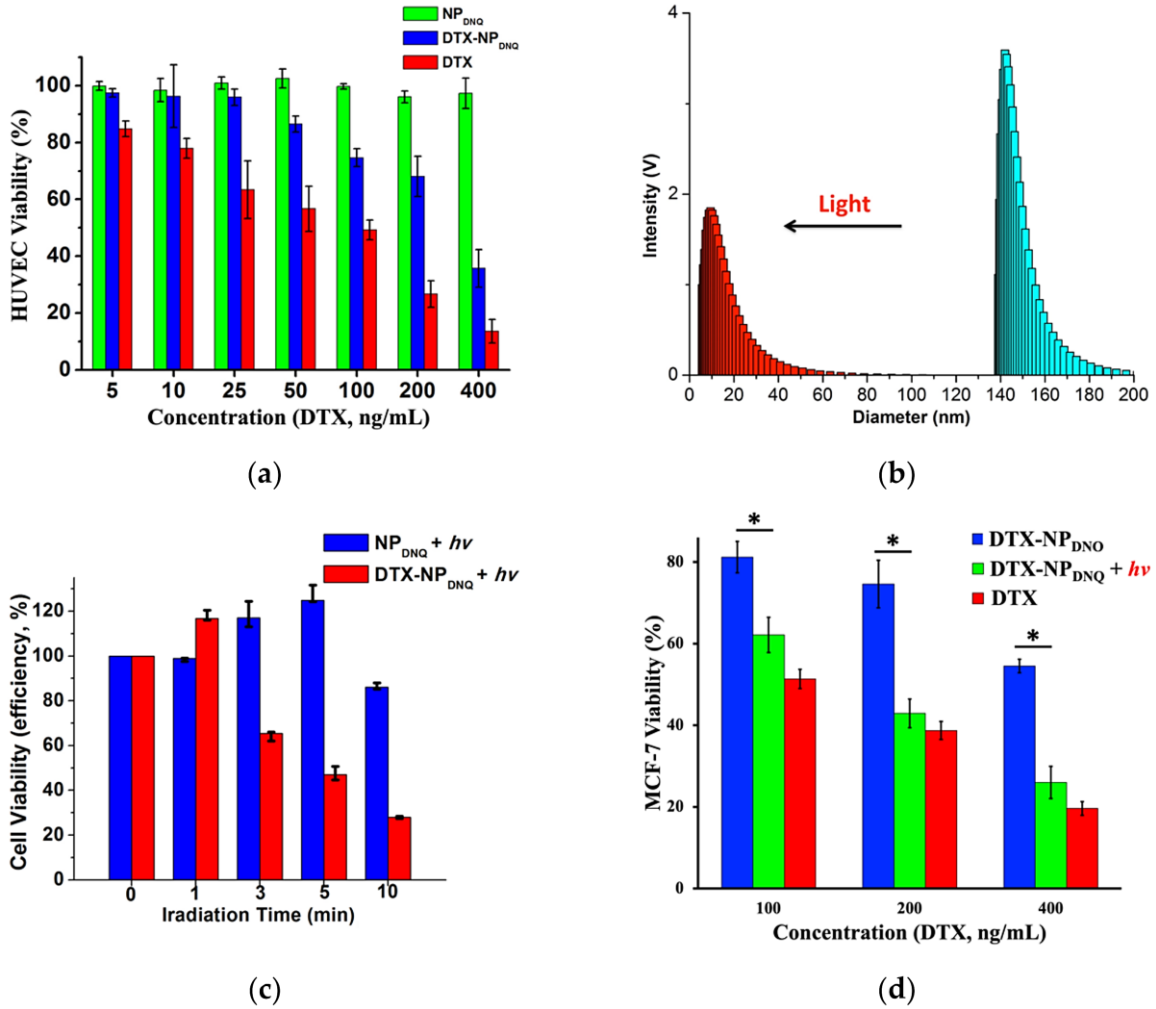

Figure 1. Cytotoxicity and stability of the prepared polymeric micelles [5]

Magnetism-responsive polymeric micelles are a kind of polymeric micelles which typically combine therapeutic payloads with magnetically active components, and can be used not only to target tumors under external magnetic fields, but also for temperature increases caused by alternating magnetic fields to prompt rapid drug release. For the cure of cancer, magnetism-responsive polymeric micelles show a great potential. Superparamagnetic iron oxide nanoparticles represent the magnetism-responsive nanoparticles with the size less than 10 nanometers. Normally, magnetism-responsive polymeric micelles act under a double stimulus such as pH and magnetism dual-responsive. For example, Ren et al. prepare a kind of dynamic covalent Fe_3O_4 nanoparticles which are dual-responsive by pH and magnetism in paraffin in water pickling emulsion [6]. This kind of polymeric micelles which contains a Fe_3O_4 core can separate the oily drugs from emulsions under the effect of an external magnetic field. Endowed polymeric micelles with multiple stimulus responses can effectively control their stability and broaden their application range.

2.2. Temperature and ultrasound response

Temperature is extensively researched stimuli of drug release. It can be either an exogenous stimulus or an endogenous stimulus. Generally, temperature is defined as an expgenous stimuli. For instant, poly(N-isopropylacrylamide) is the most typical temperature-responsive polymeric micelle. Temperature-responsive polymer micelles contain temperature-responsive block polymers whose size and structure change dramatically in response to temperature changes, thereby destabilizing the micelles to trigger drug release. Block polymers would be divided into two classes. The first kind of temperature-responsive polymeric micelles are composed of temperature-responsive polymer structures as copolymers of hydrophilic and hydrophobic chain segments. These segments can be used to prepare the desired polymers-based functional materials, which is with temperature-responsive polymer chain segments as shell and hydrophobic chain segments as core layer. What's more, another type of temperature-responsive polymer micelles is temperature-responsive polymer structure, which is a copolymer composed of hydrophobic and hydrophilic chain segments. Temperature-responsive polymers micelles tend to process phase change at a right temperature, which is called the lowest boundary solution temperature (LCST). For example, when the temperature is lower than the LCST, the hydrophilic part of the polymer and water molecules does not change. Due to the action of hydrogen bonds and van der Waals forces, the polymer water molecules are formed around the solvation shell, which are connected together by hydrogen bonds. The polymers have a stretched filament-like structure and exhibit water-soluble properties. Miyata et al. prepared amphiphilic liquid crystalline polymers, which contains side-chain [7]. At body temperature, liquid crystalline polymers-g-oligo (ethylene glycol) can undergo a nematic-isotropic phase transition. The prepared micelles would be suppressed when temperature is less than the phase transition temperature. And anticancer drugs would release when the temperature is higher than phase transition temperature. As shown in Figure 2, fluorescein was used as a target drug. The results show that the drug release rate of the prepared micelles is affected by temperature. The release rate constant of the drug remained constant at temperatures below the phase transition temperature (T_{NI}), but gradually increased with increasing temperature at temperatures above the T_{NI}.

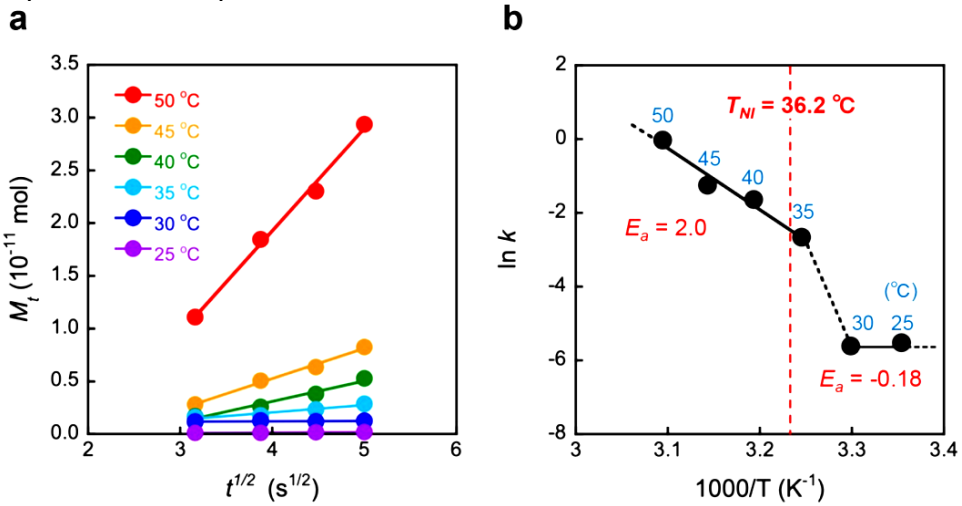

Figure 2. Temperature-responsive release for fluorescein by using the prepared micelles [7]

Ultrasound-responsive polymeric micelles have plenty of advantages such as convenient administration, low budget and deep penetration, so it has been proved that it's an effective way in the field of drug delivery. Ultrasound can promote cellular uptake of drugs by increasing the permeability of biological barriers (e.g. membranes, mucous membranes) by forming cavitation bubbles and generating heat. Ultrasound-responsive polymer micelles have been shown to cause physical or chemical damage to the micelles in response to ultrasound, thereby increasing drug release. The biggest nature of ultrasound-responsive polymeric micelles is its non-invasive nature. One challenge that researchers concentrate on is its site-specificity. However, the non-toxic pathway makes it possible to deliver the drug. The mechanism of ultrasound-responsive drug delivery is

divided into two categories, one is thermal effect and the other is non-thermal effect. Non-thermal effect usually associates with cavitation activity which enables polymeric micelles become more permeable. With the help of ultrasound, the micelle system exhibited time-dependent tumor-targeted deposition after systemic administration due to enhanced permeability of the tumor region and increased micelle penetration in irradiated tumor cells under the effect of ultrasound.

3. Endogenous stimuli-based polymeric micelles

3.1. Redox response

Redox-responsive polymeric micelles are extensively used in the tumor cells. They are able to release the drugs by doing some redox reactions. Due to differences in glutathione concentrations, redox potential is considered a feasible biological indicator to differentiate between extracellular and intracellular environments and between tumors tissues and normal tissues. A lot of tumor tissues were found to be reduced and highly hypoxic compared to healthy tissues, with intracellular glutathione concentrations that are more than four times the concentration of normal cells. From former research [8], a large proportion of redox-responsive polymeric micelles work by incorporating disulfide bonds in or between hydrophobic segments and hydrophilic segments. It is well-known that many anti-cancer drugs play their roles only inside cells, such as in the cytoplasm and nucleus. This is beneficial to release the drug from the polymeric micelles. For instant, Yan et al. makes progress in redox-responsive polymeric nanomaterials.

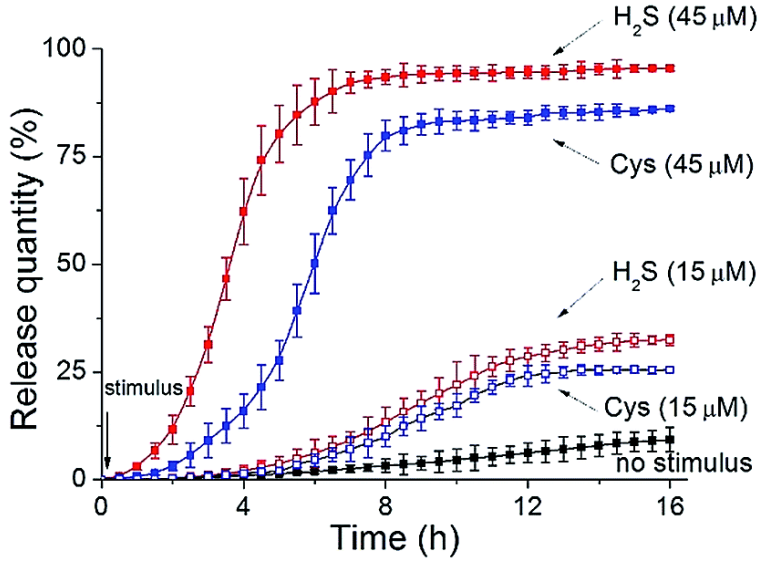

Figure 3. Drug release behavior under different stimulus conditions [8]

Yan et al. prepared a o-azidomethylbenzoate-based responsive micelles by using hydrogen sulfide (H_2S) as a foreign stimulus molecule [8]. As show in Figure 3, the prepared polymeric micelles can respond to hydrogen sulfide(H2S), it leads to make the release of drug more controllable. In the absence of any trigger, the prepared material exhibited a lower free release, less than 10% over 16 hours. When a low concentration of H_2S stimulation (15 μM) was applied, the release rate increased, approaching 32% within 16 h. When a higher concentration of H_2S stimulator (45 μM) was added, the release rate increased further, reaching 94% in a shorter time (6 h). Zhang et al. developed a progressive polymer-camptothecin (CPT) prodrug that contains a diblock polyphosphoester. After being modified by carrying out “click chemistry” reaction, the polymeric micelles have the ability to self-assemble to special polymeric micelles in the solution [9]. The results show that this polymer micelle-type functional material based on glutathione reaction has good application potential for cancer treatment.

3.2. pH response

The pH is one of the most commonly used and important physiological index to evaluate the metabolic degree of specific tissues [10]. For example, normal tissue has a pH of around 7.4, while extracellular of tumor tissue has a pH value of around 6.8, and intracellular pH value of tumor tissue is between 5.0 and 6.0. When polymeric micelles can respond to falling gradient in the pH of tumor cells. pH-responsive drug delivery carriers, are stable in normal physiological pH and extracellular fluid of normal tissues. After receiving the stimuli, polymer micelles change its structure and its properties (e.g. conformation, hydrophilicity/hydrophobicity, solubility and volume). As a drug delivery vehicle, pH-responsive polymer micelles are able to selectively release drugs at specific positons and make drugs accumulate in local areas, so as to enhance the therapeutic effect of drugs and reduce damage to normal tissues.

For synthesis of pH-responsive polymer micelles, there are two tactics. The first way is to introduce ionizable group (e.g. Weak bases, weak acids and polyelectrolytes) into the polymer backbone. For example, polyelectrolytes are the common pH-responsive polymers, which contains ionic functional groups. As the pH of the environment changes, the degree of ionization of these functional groups also changes, which in turn induces the phase transition of the polyelectrolyte, which has a great influence on the solubility of the polyelectrolyte. The second way is to introduce pH-sensitive bonds (e.g. ester bond that will hydrolyze under acidic conditions). For instance, Gao et al. synthesizes a kind of pH-responsive micelle which encloses photothermal polydopamine-nanoparticles (PDA-NPs) [11]. As shown in Figure 4, using *S. aureus* as the target bacteria, the prepared pH-responsive micelles can effectively target and eradicate infectious biofilms. Photothermal combined with a pH-responsive construction strategy could enable polymeric micelle-based functional materials as a novel infection control strategy for clinical application.

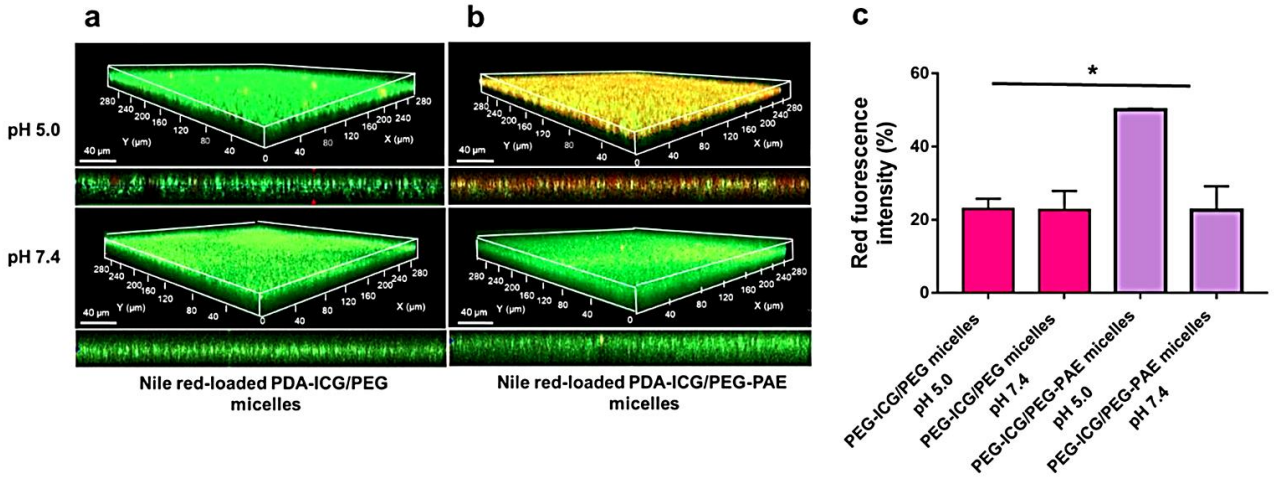

Figure 4. Effects of the prepared polymeric micelles on the growth of *S. aureus* in biofilms under different pH conditions [11]

3.3. Enzyme response

It is well-known that enzymes are a class of extremely important biocatalyst. Enzymes play an important role in many enzymatic chemical reaction processes in the body because of their exceptional specificity to the substrate and excellent catalytic properties, they are able to catalyze a series of chemical reactions under mild conditions. Also, it is adjustable based on the experimental requirements. Dysregulation of enzyme expression is able to be found in plenty of different physiological conditions and is accompanied by many common diseases. The dysregulated enzyme has been regarded as a standard in physiology for the diagnosis and prediction of different categories and sections of cancer, and this also has a good opportunity to offer great help for bio-triggering targeted cancer therapies. To treat the cancer, enzyme-responsive polymeric micelles have plenty of superiority. Firstly, they have high selectivity to provide an opportunity for them to find the tumor tissues and target cells effectively.

What's more, they have good compatibility with the tissues of the human body in the internal environment. For example, He et al. prepared the MMP-2-responsive polymer micelles to develop a new enzyme-responsive drug delivery method [12]. As shown in Figure 5, the prepared micelles can significantly accelerate the release rate of drugs that the drug release can reach 73.2±2.05% at 12 h, indicating that they can selectively release drugs in tumors, which is very important for the development of tumor therapy based on targeted therapy. In addition, the developed enzyme-responsive drug delivery systems can be able to provide new therapeutic options for tumor treatment.

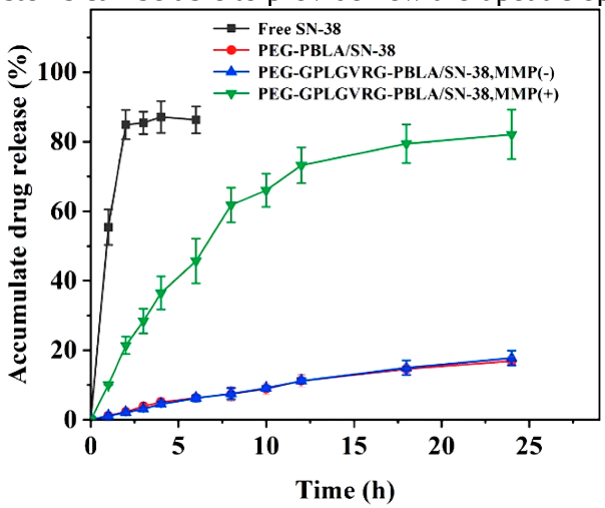

Figure 5. Accumulate drug release behavior under different conditions [12]

4. Conclusions

To conclude, the seven kind stimuli-responsive polymeric micelles which are mentioned above show their unique characteristics and advantages. A lot of clinical trials and subject studies have demonstrated that stimulus-responsive polymer micelles loaded with chemotherapy drugs are able to enhance the anti-cancer efficiency of drugs and minimize the toxicity and side effects of drugs on other normal tissues in the internal environment. Nevertheless, some points such as non-toxic, no side effects, micellar metabolism and drug delivery mechanism still need to explore and innovate. With the more and more in-depth researches and scientific and technological advance, the prospect of stimulus-responsive polymer micelles for tumor therapy is worth looking forward to.

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