Application of Degradable Polymers for the Treatment of Wounds and Tumors

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Abstract. Degradable polymers are of great significance in bacteriostatic and cancer treatment. Biodegradable biomaterials have the characteristics of high safety, good environmental protection and good therapeutic effect. This article mainly introduces the application of the polymerization strategy in the biomedical field. In the direction of bacteriostasis, degradable polymers provide a series of new and effective ideas for researchers. For example, the biodegradable antimicrobial gene vector based on tobramycin, a kind of antibiotic, coupled with polyaspartic acid (TPT) effectively realized the antimicrobial treatment and restoration of skin damage. A multifunctional injectable hydrogel dressing that integrates electrical conductivity, good antioxidant capacity and antibacterial properties has been designed to treat skin injuries. Supramolecular polymers with strong antibacterial effect and controllable degradability were used to prepare biodegradable antibiotics to enhance the antibacterial effect of antibiotics against drug-resistant bacteria. In addition, degradable polymers also show great potential in the treatment of cancer. For example, scientists have discovered that drug release can be triggered from tumor-targeted polymer nanoparticles through the process of polymer degradation mediated by reactive oxygen species. The development of a rapidly degraded chitosan based multilayer controlled release membrane provides a theoretical basis for the preparation of customized multilayer membranes for drug administration. The adoption of the concept of the macromolecular engineering, which mixes drugs with polymers, opens up a new way to design polymer biodegradable drug delivery systems. Thus, the potential of biodegradable polymers in various interdisciplinary fields has been highly valued, and they will be more widely used in production and life in the future.

Keywords: Degradable polymers, Biomedicine, Application.

1. Introduction

As synthetic polymers are now ubiquitous in the society and the demand of consumers for polymer-based products is increasing, the environmental problems caused by plastics become more serious. The applications of the synthetic's polymers bring convenience to people's life, involving packaging, medical devices and microelectronics. However, most of plastic garbage will be finally landfilled or incinerated, which is harmful to the environment. For example, until 2025, there are approximately 100-250 million metric tons of plastic waste pouring into the ocean every year, which will negatively impact the marine organisms and even disrupt the marine ecosystem. What's worse, the waste of synthetic polymers would result in toxicity and immune responses, which does harm to the health of people. Thus, effective solutions should be proposed and some strategies should be used to release the environmental pollution.

Nowadays, the concept of depolymerization strategies is proposed and it is the process of converting a polymer into a monomer, which is considered as a great way to reduce plastic pollution. The depolymerization strategies have potential applications for the recyclability of polymeric materials, making it possible that clean monomers can be reclaimed and reused to make new plastic. Biodegradable materials have special advantages over traditional materials. The materials are biodegradable, safe and environmentally friendly. What's more, some biodegradable plastics can perfectly accomplish what conventional plastics cannot, and in some applications can also completely replace conventional plastics. After being used, degradable plastics can be degraded rapidly and easily in the environment. Because of the safety of degradable plastics, the residual substances produced during degradation are harmless to the environment and human body. In this case, the degradable polymers have drawn people's attention these years. The most common biodegradable polymers include polyester, polyanhydride, polysaccharide, polycarbonate (PC), polyacetal, polyphosphazene, and so on. Degradable polymers are widely used in medical applications, such as surgical sutures, blood vessel grafts, stents, catheters, artificial skin and drug delivery systems [1]. To be more specific, there are some examples about the application of degradable polymers. Because of the overuse of antibiotics, the antibiotic-resistant bacteria are increasing these years [2]. Some traditional antibiotics like benzalkonium chloride are easily influenced by the resistance of bacteria. In order to improve biocidal activity and avoid the antibiotic-resistant bacteria, quaternary ammonium compounds (QACs), a kind of common disinfectant, can be integrated into polymer structures. Amphiphilicity is a property that can make sure polymer particles can penetrate through the bacterial membrane. To achieve amphiphilicity, polyionic liquids (PILs) is used. However, because of the poor degradability, PILs would cause the accumulation of polymers. Fortunately, through continuous research, scientists first synthesize thiimidazole PIL and small molecule. As an effective antimicrobial agent, PIL 4 can be stably degraded in water at room temperature for 3 weeks, which proves a kind of biodegradable PIL biocide by depolymerizing and losing positive charge. Thus, this method uses the biocidal activity of cationic polymer structures and simultaneously use the ability to depolymerize and deionize to achieve degradability.

Another specific application of degradable polymer is to use BC and PHA based composite materials and implants to repair tissue defects [3]. It is known that the materials that make wound recover should have some practical properties, such as regenerating themselves and maintaining blood supply. As the promising biomedical materials, bacterial cellulose (BC) and bioabsorbable polyhydroxyalkanoates (PHAs) have aroused people's interest. BC has high biocompatibility, high mechanical strength and good air permeability, which can be used to reconstruct skin defect. And P(3HB/4HB) is biodegradable and highly biocompatible, which can be used in biomedical applications. Through a series of experiments, scientists have proved that based on BC and P(3HB/4HB) combined with wound healing drugs and cells, biotechnological wound dressings are very effective in skin wound treatment. The historical polymerization methods include step growth and chain growth polymerization, which are common production methods. The predominant approaches are open-loop polymerization reaction of cyclic esters and N-carboxyanhydrides, and ring-opening polymerizations of cyclic ketene acetals [4]. Currently, olefin metathesis polymerization is an efficient way to increase the types of biodegradable polymers. Besides, olefin metathesis polymerization can make polymers adapt to different functional groups, thus scientists can incorporate conceivable degradable moieties into suitable monomers and then into polymer skeletons, which is an important approach to synthesize a wide range of degradable polymers like polyester. The olefin metathesis polymerization mainly includes acyclic diene metathesis polymerization, entropy-driven and enthalpy-driven ring-opening metathesis polymerization, as well as cascade enzyme metathesis. Therefore, this article will analyze the application of different types of degradable polymers in the biomedical field, such as for cancer treatment, treatment of skin infections caused by bacteria.

2. Application of polymers in biomedicine

2.1. The wound infection

With widespread use and even abuse of antibiotics, the problem of bacterial resistance has become very serious [5]. Bacterial resistance would increase during long-term therapy and drug-resistant bacteria would cause serious infections, which are very harmful to human health. To solve the problem of antibiotic resistance, supramolecular antibiotics have been used. Supramolecular polymers are polymers linked by non-covalent interactions between many monomers, and the non-covalent interactions are reversible. Thus, compared with ordinary antibiotics, supramolecular antibiotics are biodegradable and reversible. The application of supramolecular antibiotics can reduce the production of drug-resistant bacteria by controlling the antimicrobial properties. Some scientists expect to link many small molecules of antibiotics together to form supramolecular polymers, and this enrichment effect can effectively enhance the antibacterial effect of antibiotics. At the same time, because the supramolecular interactions are reversible, the supramolecular polymer is degradable. During the experiments, researchers find that if a kind of side-chain antibacterial supramolecular polymer with the polymeric backbone as the side chain can be designed, the enrichment of antibacterial effect can be realized and the antibacterial property of the polymer can be improved, as shown in Figure 1. Supramolecular polymers are usually composed of a polymer skeleton and side chain antibacterial agents. In the experiment, diffusion ordered spectroscopy (DOSY) and isothermal titration calorimetry (ITC) were used. The formation of supramolecular polymer backbone is proved by DOSY and analytical ultracentrifugation proved that antibacterial supramolecular polymer with side chains formed in the experiment. Besides, the degradability of supramolecular polymers is reflected in the ability to turn off the antimicrobial activity of antimicrobial supramolecular polymers to avoid long-term drug exposure. The antibacterial effect of this polymer can be regulated from high activity to low activity.

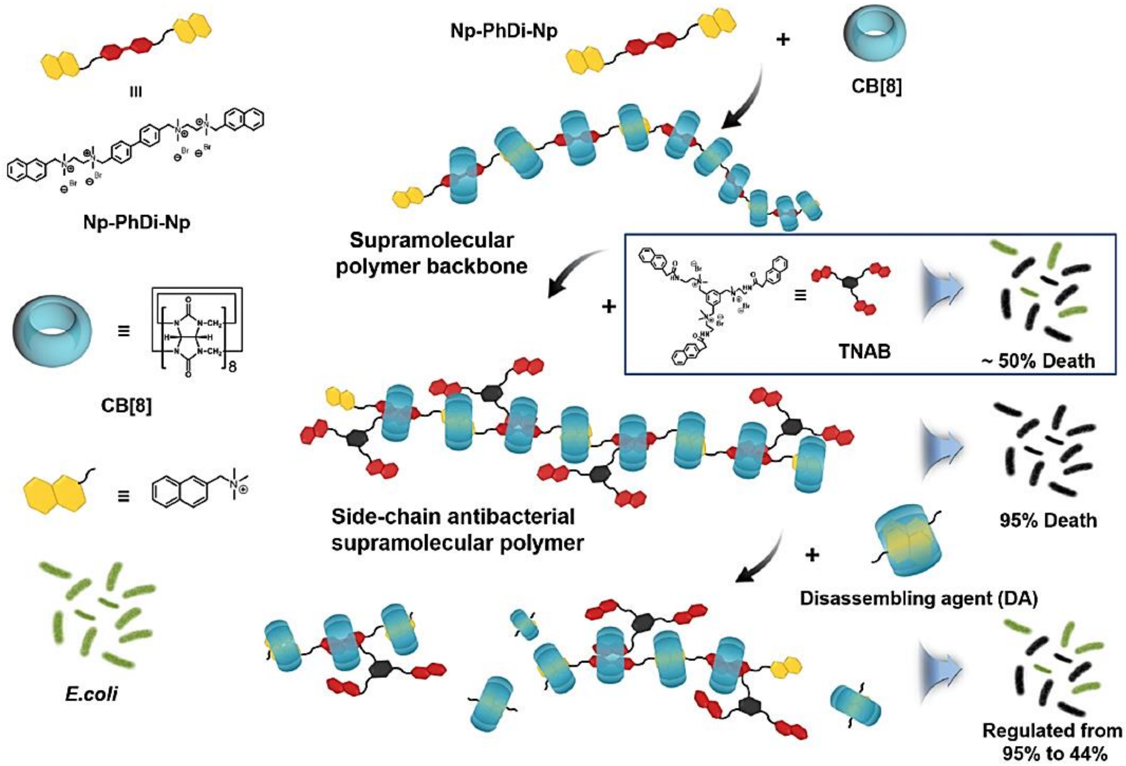

Figure 1. Schematic illustration of the chemical structures of the building blocks and the preparation of the polymers [5]

To solve the problem of skin defects caused by burns and excisions, epidermal growth factor (EGF) binds to the EGF receptor to help the tissue heal [6]. The EGF can promote skin regeneration by stimulating the proliferation and migration of keratinocytes. Although EGF can promote wound healing, protease degradation makes it difficult to maintain biological activity. As a result, researchers are looking for a more effective treatment. A functional nucleic acid (NA) has attracted attention. As shown in Figure 2, researchers hope to find a high-performance antimicrobial NA vector to successfully implement gene therapy. In recent years, a degradable antimicrobial PAsp derivative (TPT) based on tobramycin conjugation has been proposed as an effective nanoparticle system encoding EGF (pEGF) to achieve antimicrobial treatment and the restoration of skin defects or skin infections. The advantage of TPT is that it can be degraded in acidic, glycosidase or lactamase environments. The experimental results showed that tobramycin caused the open-loop polymerization of BLA-NCA, and then has amination reaction with tobramycin. The biodegradable antimicrobial vector based on tobramycin coupled with PAsp derivatives was eventually made. The vector has the advantages of good degradation, low cytotoxicity and good blood compatibility. It also showed good infectious performance, and its pEGF transmission ability promoted the proliferation of fibroblasts. Therefore, the biodegradable antimicrobial vector (TPT) is of great significance for the treatment of infected tissue defects.

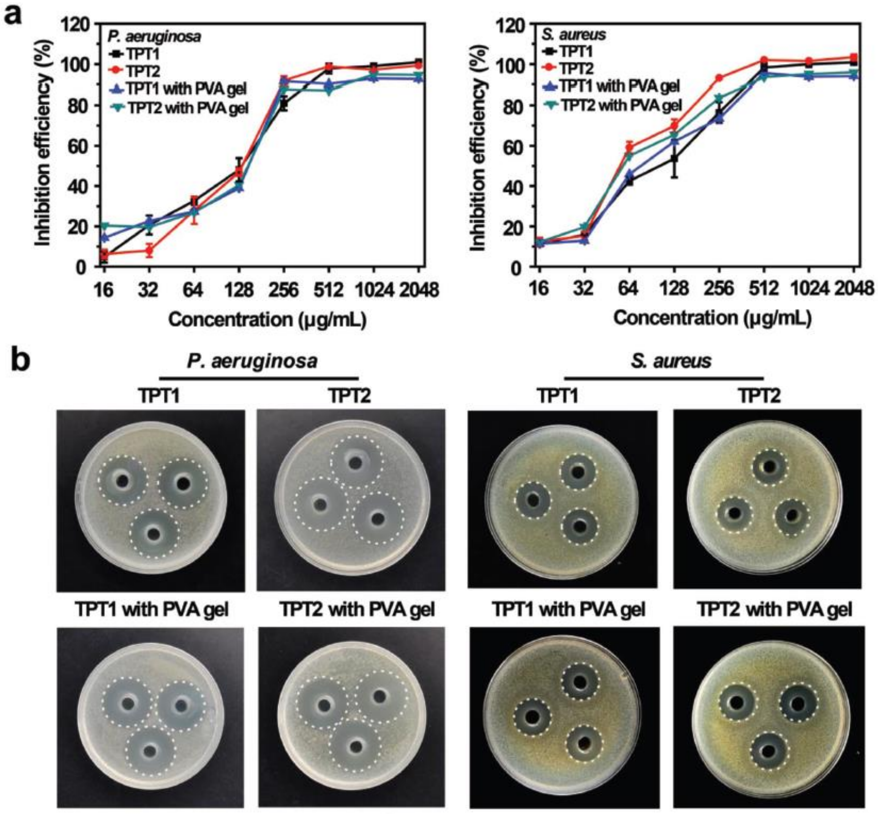

Figure 2. Antibacterial effect of prepared polymer materials [6]

Recently, new functional dressings have attracted more and more attention from material engineers [7]. Protective dressings allow for rapid wound healing and accelerate the recovery of skin barrier function. Commonly used biomaterials include electrospun nanofibers, biocompatible membranes, and functional hydrogels. Loose and easily absorbed hydrogels content can absorb a large number of exudates or blood, which can keep good oxygen permeability and water permeability while blocking microorganisms. Hydrogels that can be injected and have biodegradable polymers are therefore good choices. Hyaluronic acid (HA), because it's harmless to the environment and has high degradability, can be used to prepare this new kind of gels. But it doesn't have the versatility to heal wounds and stimulate cell repair. Conducting polymers were shown to accelerate the process of tissue repair by promoting cell growth, proliferation and differentiation. Thus, the design of new functional wound dressings with electrical conductivity will be more conducive to promote the wound healing process. Researchers expect to design wound coatings either by injecting antimicrobials into the coatings or by using antibacterial materials. Aniline oligomers have good structural design, good electroactivity and solubility, and can be cleared by the kidney in the physical environment. Amoxicillin, an antibiotic with highly effective antimicrobial properties, was embedded in hydrogels in situ to improve the antimicrobial properties of this kind of conductive hydrogel coatings. In the experiment, researchers prepared a kind of conductive antioxidant hydrogel dressings that can be degraded and injected, which have ideal wound-healing multifunctional properties. In addition, the hydrogel being injected with amoxicillin has good antibacterial effect. The *in vivo* therapeutic effect of the hydrogel coating was evaluated by wound shrinkage area and pathological examination results. The experimental data show that the multifunctional OHA-A T10/CEC hydrogel can effectively help healing of wounds and is expected to be a bioactive dressing for skin wounds.

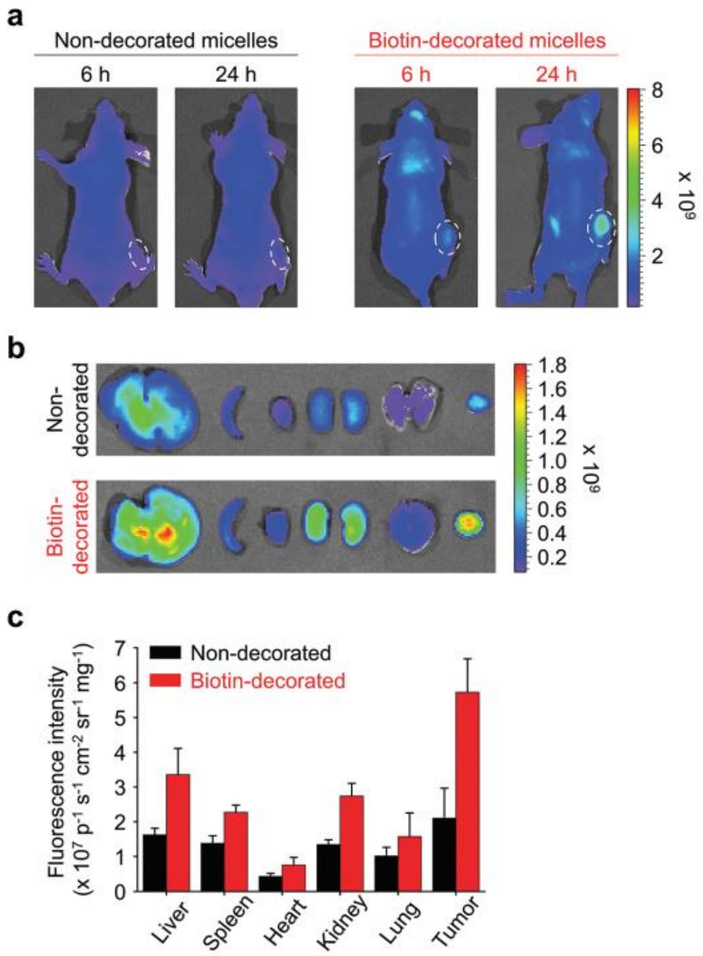

Figure 3. Distribution of prepared micelles *in vivo* [8]

2.2. The tumor treatment and drug delivery

In the medical field, tumor-targeted nanocarriers continue to develop. To increase local drug concentrations in tumor tissues to reduce side effects, researchers hope to enhance the targeting of anti-cancer drugs [8], as shown in Figure 3. Using this method, scientists can improve the maximum tolerated dose and decrease the minimum effective dose of anti-cancer drugs. However, the complexity of tumor physiology leads to the inefficiency of nanocarriers, and just a small portion of nanocarriers being infected accumulate in tumor tissues. In order to increase the efficiency of the carriers into deep tumor tissues and make anticancer drugs diffuse freely in tumor tissues, researchers have studied stimulus-sensitive nanocarriers. Light is an easily controlled stimulus. Photosensitive nanocarriers can release anticancer drugs when photochemical bonds break in the photoactive fraction. Photodynamic induced drug release is a new phototriggered drug release mechanism, which has attracted the attention of researchers. The photosensitizer can generate reactive oxygen species (ROS) to decompose the degradable part of the nanocarrier for releasing drug. However, the drawbacks of such photosensitive nanocarriers are that they require high doses of anti-cancer drugs, and their therapeutic effects are difficult to scale up to organs that cannot be reached by endoscopes and laparoscopes. The researchers hope the nanocarriers will be able to efficiently deliver cancer drugs at low concentrations and light intensity. Recently, a NIR kinetic approach has been proposed to make anti-cancer drugs work better and more efficiently by delivering drugs on demand from cancer-targeted nanocarriers. The SiNc can be used as near-infrared photosensitizer because of its high hydrophobicity and high infrared absorption rate. The researchers expect to use the photodynamic release kinetics of paclitaxel to enable incorporation of biotin-PEG-b-PPADT micelles for better performance. Through experiments, the scientists demonstrated that polythionone-based ROS can degrade the micellar encapsulation of SiNc effective anti-cancer in vivo. To prove the effectiveness of NIR photosensitive micelles in vivo, tissue-like phantoms simulating thick biological tissues were used. In the presence of a tissue-like phantom, polythioketal micelles decorated with illuminated biotin exhibit cytotoxicity similar to that of paclitaxel. The experimental results show that photodynamic chemotherapy can be effectively used to treat cancer in deeper tissues.

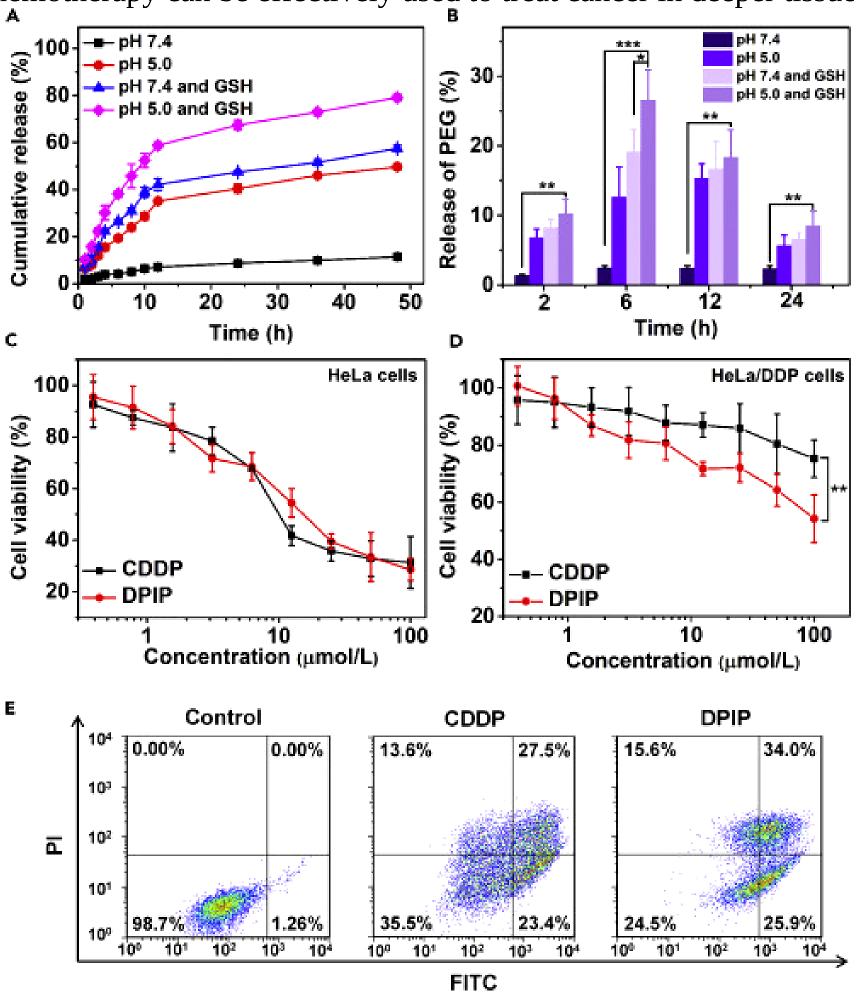

Figure 4. *In vitro* degradation and anticancer effects of prepared materials [10]

To address the issues of drug dosage, efficacy and safety, researchers are focusing on the development of intelligent drug delivery systems (DDS) to control drug delivery [9]. During the treatment, drug release should be predictable. Because drug concentrations above the toxicity threshold can cause harm to patients, while drug concentrations below the subtherapeutic threshold are ineffective. Thus, the researchers want to reduce drug use, minimize side effects and toxicity, and extend the duration of treatment to improve treatment effectiveness. In order to control and provide controlled medication release, assembling layer by layer was found to be an efficient platform preparation technology. This technique can combine multiple polyelectrolytes to produce multilayers. Some properties of the multilayers can be effectively controlled by changing conditions, the properties include structure, pore size and porosity. Natural polymer has better biocompatibility and biodegradability than synthetic polymer, which is more suitable for building drug delivery platform. However, high pH and salt levels can reduce the stability of the multilayer and allow the drug to flow out of the membrane. Therefore, researchers have studied the membrane structure, stability and functional group density of multi-layered films to prepare a biocompatible platform to deliver drugs which can control the release of drugs. Chitosan (CHI)-based multilayer membranes in which the CHI is mixed respectively with hyaluronic acid (HA), alginic acid (ALG) and tannic acid (TA) was designed. CHI is a linear polysaccharide, a natural polysaccharide from the shell of crustaceans. The HA is a glycosaminoglycan, which is non-sulfated. It has a great effect on cell migration and proliferation and is often used to treat malignant tumors. ALG is a weakly acidic phenol, a natural polysaccharide. Besides, TA is a weakly acidic polyphenol and is generally extracted from plants, which has antibacterial properties for cancer treatment. The researchers designed a chitosan/hyaluronic acid multilayer membrane with a nanopore structure, and some small molecules can be diffused through the structure. In the experiment, scientists designed three different types of chitosan-based multi-layered membranes. The CHI/HA film has a nanopore structure with CHI chain diffusion during deposition; Chitosan/alginic acid films have a compact structure that includes highly ionized alginic acid chains and many carboxyl groups deposited in the multi-layer membrane. The CHI/TA film have a structure with large pores and deposited CHI chains that rarely ionize. In experiments, researchers have noticed that the chitosan-based multiple membranes can efficiently deliver drugs, and the release of drugs can be controlled according to the properties of the components. Therefore, fine-tuning the efficacy is feasible. The study demonstrated the accurate control of the release of drugs by CHI's multilayer membrane, showing potential as a platform for cancer therapy.

Macromolecular engineering is used to design different types of polymers with different characteristics and is of great use in various fields [10]. When transporting drugs, macromolecular engineering has tunable physical and chemical properties that allow the preparation of custom macromolecules with a wide variety of compositions and chain lengths as required. However, this polymer material also has some problems, such as low clearance rate, inflammatory reaction and so on. To solve the problem of polymer carrier safety, scientists want to build safer and more efficient polymer DDS. The concept of hybrid macromolecular engineering of drugs and polymers has been proposed to create a convenient, degradable polymeric nanomedicine for anticancer drug delivery. This simple, degradable polymer nanomedicine consists of polyethylene glycol (PEG) polymer and an anticancer platinum (IV) prodrug. Degradable DPIP can be combined with platinum (IV) [DPIP], and the target product can be gotten by condensation reaction with the degradable monomer. With the degradation of DPIP, the side effects of the polymer carrier can be eliminated. Cell accumulation of platinum (IV) prodrugs is promoted by introducing phenylketone groups to increase lipophilicity. Since the unstable hydrazone chain is prone to hydrolysis in the weakly acidic environment of the endosome, the polymer can be broken down after uptake by cancer cells. *In vitro* cell experiments were carried out to evaluate the therapeutic efficacy of DPIP. From the results, it was shown that DPIP was highly toxic to tumors and low toxic to normal tissues. It was also revealed that amphipathic DPIP accumulated more around the tumor and had a good therapeutic effect, as shown in Figure 4. Besides, metabolic experiments showed that DPIP could be degraded to PEG by tumor environment and expelled from the body in a relatively short time. In addition, DPIP has no long-term toxicity *in vivo*. Therefore, this protocol can not only keep the strengths of PEG, but also improve the properties of the drug, reducing the non-biodegradable side effects of PEG. It was proved that the novel biodegradable PEG delivery nanosystem could self-assemble and accumulate significantly on the tumor. The mixture of PEG and CDDP-1 allows DPIP to auto-assemble and accumulate significantly on tumors through EPR effects. Then degraded drugs released from DPIP can effectively inhibit tumor growth. This elaborate macromolecular engineering design successfully constructed a kind of simple, tunable, and safe polymer nanomaterials through the hydrophilic and hydrophobic changes of anti-cancer drugs and carriers of biodegradable polymer during conveying process. This biodegradable pharmaceutical polymer design could be an effective means of treating cancer due to its excellent performance in terms of safety, efficiency and bioavailability.

3. Conclusions

In conclusion, this paper introduces the significance of the emergence of degradable polymer and its far-reaching influence on people's life. By demonstrating the specific application of biodegradable polymers in the fields of bacteriostatic and cancer treatment, it demonstrates the unique advantages and great prospects of the polymers. Although biodegradable materials still have some problems, such as difficult to synthesize and control, with the development of science and technology and continuous research by researchers, more efficient methods will be found in the future. Biodegradable polymers have shown great potential and there is no doubt that research on them will continue.

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