



齊魯工業大學  
QILU UNIVERSITY OF TECHNOLOGY

## 本科毕业设计(论文)

Synthesis and Characterization of Tetraphenylethylene-  
based Amphiphilic Copolymer as Novel Drug Carrier

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# Synthesis and Characterization of Tetraphenylethylene-based Amphiphilic Copolymer as Novel Drug Carrier

## 以 T P E 为基础的 两亲性嵌段聚 合物作为新型药物载体的合成 与表征

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## ABSTRACT

Tumor drug treatment is one of the hot topics in modern society, and it has great potential for nanomaterials as drug-carrying systems. Most traditional fluorescent materials emit strong fluorescence in solution, but the fluorescence becomes weak in the aggregate state, and even quenched. Hexaphenylsilole emits a strong fluorescence in the aggregate state, which is completely opposite to the ACQ phenomenon. This kind of phenomenon in which weak fluorescence is emitted in the solution and the fluorescence intensity becomes stronger in the aggregate state is called "aggregation-included emission" (AIE). Such materials provide a strong and beneficial help for chemotherapy. Amphiphilic block polymers can be loaded with a variety of insoluble tumor drugs, and nanocarriers can become one of the hotspots of contemporary drug system research by virtue of their retention and accumulation advantages. Therefore, it is of great significance to develop a new type of amphiphilic nano drug carrier with aggregation-induced luminescence effect. In this paper, tetraphenylethylene (TPE) is used as a material, based on the research theory of Academician Tang Benzhong and others, using experimental characterization data for comparative analysis, and synthesis a novel amphiphilic copolymer drug carrier.

Key words: ACQ; AIE; Chemical Therapy; Tumor Treatment; Amphiphilic

## 摘 要

肿瘤的药物治​​疗是现代社会的热门话题之一，对于作为载药系统的纳米材料有着极大的潜力。大部分过去经常使用的荧光材料在溶液中会发出较强的荧光，却在聚集态时发生荧光的消减更有甚者会直接猝灭。六苯基噻咯在聚集态下发出了强烈的荧光，这与 ACQ 现象完全相反。这类在低浓度状态时仅发出微弱荧光，在聚集态时荧光强度变强的现象被称为“聚集诱导发光”（Aggregation-included Emission, AIE）。这类材料为化学治疗提供了强有力的帮助。具有两亲性的嵌段聚合物能装载多种难溶的肿瘤药物，而纳米载体可以凭借它的滞留和堆积优势，成为当代药系统研究的热点之一。所以研发新型的、具有聚集诱导发光效应的两亲性纳米药物载体具有十分重要的意义。本文就四苯基乙烯（TPE）作为材料，根据唐本忠院士等人的研究理论，应用实验表征数据进行比较分析，制作新型两亲性嵌段聚合物载体。

关键词：AIE 两亲性 四苯基乙烯 纳米材料 癌症治疗

# Chapter 1. Introduction

## 1.1 Primary Introduction

Light, whether in human daily life or technological development, plays a vital role. Since ancient times, human beings have never stopped studying optics. In modern optical research, luminescent materials gradually occupy a key leading position in scientific research and are used in various fields. [1-3]

In modern society, fluorescent materials have gained a lot of favor from scientists due to their low price, low toxicity, simple operation, and easy structure adjustment and manipulation. [4-9]

## 1.2 AIE Materials

### 1.2.1 About AIE Materials

AIE materials have a bright future. Traditional fluorescent materials will emit strong fluorescence under solution conditions, but only weak fluorescence in the aggregate state. This phenomenon in which a large amount of fluorescence can be emitted in solution, and the fluorescence weakens or even disappears in the solid state is called "aggregation-caused quenching" (ACQ).<sup>[10]</sup> In 2001, the chemist Chen Benzong and academician of the Hong Kong University of Science and Technology Professor Tang's students inadvertently discovered that hexaphenylsilole emits a strong fluorescence in the aggregate state, which is completely opposite to the ACQ phenomenon. After a series of studies, the phenomenon that molecules that emit weak or even non-luminescent fluorescence in the solution increase their fluorescence after aggregation is named "aggregation-induced emission" (AIE). Compared with ACQ material, AIE material has better characteristics of biological imaging and targeted delivery, showing a bright future in various aspects of scientific research.<sup>[11]</sup>

Common AIE materials include Tetraphenylethylene (TPE) and Hexaphenylsilole (1,1,2,3,4,5-Hexaphenylsilole, HPS). The earliest discovered AIEgen is hexaphenyl silole, the benzene ring can rotate relative to the silole nucleus through a single bond. Tetraphenylethylene is a widely studied AIE material. Although it has a significantly different molecular structure from HPS, it is essentially similar in structure. After discovering for the first time that hexaphenylsilole has the AIE effect, Tang Benzong's research team has successively designed and synthesized a series of HPS derivatives. [12]

The study found that the properties of AIE are common to these compounds. The team members analyzed the molecular structure of HPS derivatives and found that the aromatic substituents at the center and the periphery of the silole are connected by a rotatable carbon-carbon single bond, which is the common point of the molecular structure of these compounds.

AIE materials have many characteristics, such as strong luminescence characteristics in solid state; strong stability to ultraviolet excitation light; it can produce very high-resolution images in cell imaging and related biological imaging technology; the higher the concentration, the stronger the luminescence; in the solid state or high concentration, it has a very high sensitivity; flexible chemical modification can be used to achieve different wavelengths of luminescence control.

AIE nanomaterials have received more and more attention in the field of fluorescence imaging due to their high luminous efficiency and excellent resistance to photobleaching. In 2016, "Nature" magazine evaluated 4 important bio-nano imaging materials in the current scientific research field, including AIE nanomaterials and quantum dots, semiconductor polymer dots and up-conversion nanoparticles. It can be seen that AIE materials are getting more and more. To the attention of scientists all over the world. [13][14]

Among them, the most significant advantage of AIE materials is that they can emit light efficiently in the aggregated state, and the aggregated state is the most widespread form of luminescent materials in practical applications. Since the discovery of aggregation-induced luminescence (AIE), the team of Academician Tang Benzhong began to search for AIE materials that are the opposite of luminescence quenching, and have successively developed many AIE systems and materials, realizing the use of AIE materials in optoelectronic devices, smart materials, chemical sensing, and Applications in the fields of biosensing and imaging. The phenomenon of aggregation-induced luminescence is an original concept first proposed by Chinese scientists, which has opened up a new field of organic luminescent materials.

#### 1.1.2 The Development Status of AIE Materials both domestic and overseas

Academician Tang Benzhong of the Hong Kong University of Science and Technology and his students inadvertently discovered that the AIE effect opposite to ACQ

occurs on hexaphenylsilole. Hexaphenylsilole emits intense fluorescence in the aggregated state. And successively synthesized a series of materials with AIE effect.<sup>[15]</sup>

Modern scientists mostly use fluorescent nanomolecules with fluorescent effects to target tumor cells, thereby improving the specific recognition of AIE molecules for tumor cells.

Li et al. researched and developed star-shaped amphiphilic  $\beta$ -cyclodextrin ( $\beta$ -CD) copolymer nanocarriers to overcome the problem of poor drug-carrying performance and poor water solubility of ( $\beta$ -CD). The secondary hydroxyl group of ( $\beta$ -CD) is methylated to improve solubility. The secondary hydroxyl group is coupled with mPEG-b-PCL-SH through a disulfide bond to enlarge the hydrophobic cavity and enhance the stability of the nanocarrier. Related to the nanocarrier developed by Li's research team is the EPR effect: the high permeability and retention effect of solid tumors. Compared with normal tissues, molecules or particles of certain sizes are more effective. It tends to accumulate in the nature of tumor tissue. The nanocarriers they studied can accumulate at the tumor site through the EPR effect, and release drugs in a controlled manner in the tumor-reducing microenvironment, so that premature leakage and side effects can be ignored. CCPP-2 has shown great potential as a smart and efficient anti-cancer drug delivery nanocarrier.<sup>[16]</sup>

Based on the azo reductase reaction, Yuan et al. synthesized a new type of polymerization-induced emission (AIE) fluorescent probe, which combines tetrastylene (TPE) azo groups in hydrophilic and hydrophobic (PEG and PCL) between the chain segments. In the phosphate buffer solution, the azo group has a quenching effect on TPE and has no fluorescence. In the presence of a reducing agent, the azo bond is destroyed and the assembly is broken into PEG and PCL fragments. As the degree of decomposition becomes larger, the AIE effect of TPE is activated because part of TPE is encapsulated in the final PCL aggregate. In addition, amphiphilic polymers can encapsulate drugs, such as doxorubicin, to form drug-loaded textbooks in lead solutions. Under the action of the reducing agent, the micellar fluorescence increases with the release of the drug. This amphiphilic block polymer may be used in biosensing and drug delivery under colonic conditions.<sup>[17]</sup>

He's team discovered a new family of amphiphilic copolymers, P (LMAy-co-TPEz) and PNMP<sub>x</sub>-b-P (LMAy-co-TPEz).<sup>[18]</sup> The research results show that as the length of the former increases, the latter copolymer will gradually change from water-soluble to oil-soluble. In addition, these copolymers can also self-assemble and reverse-assemble. Due to the presence of TPE fragments, their fluorescence yield significantly depends on the polarity of the solution and the morphology of the assembly, so it has good bioimaging performance.

Zhao et al. used TPE to create a new type of amphiphilic aggregation-induced emission (AIE) molecule.<sup>[19]</sup> The smart nanometers they made that form the active ingredients of liposomes through self-assembly with phospholipids have a good response at temperatures below 50°C. In addition, in vitro imaging shows that it has potential applications as a drug delivery system in the field of biomedicine.

Wu's team and became a new type of azo amphiphilic alternating copolymer P (EG4-a-NAzoOMe), which can correspond to different pH.<sup>[20]</sup> By adjusting the initial concentration, P(EG4-a-NAzoOMe) can self-assemble into uniform micelles (LCMs) of different sizes. LCMs respond to ultraviolet light as fast as this polymer, and the size of LCMs increases with the acidity of the solution, and the color changes from yellow to purple. In addition, due to the special alternating amphiphilic structure, LCMs also have AIE feature. This makes this alternating copolymer not only used as a promising adjustable carrier or sensor, but also has enlightening significance for the development of azobenzene AIE materials.

### **Introduction to Tetraphenyl Ethylene**

Tetraphenylethylene is abbreviated as TPE. Because of its high selectivity and low detection limit, TPE fluorescent probes are widely used in the field of chemical sensing, including ion detection, explosive detection, pH detection and partial gas detection. and many more.<sup>[21-23]</sup>

As biological probes, a large number of TPE units that can be combined with various biomolecules have been developed in China. The application of such probes in medical detection fields such as biomolecular sensing, bioimaging and drug release is very

important. It is of great significance to promote contemporary medical diagnosis and treatment of some related diseases. [24-26][27]

### **1.3 Nano Materials**

#### **1.3.1 the Features of Nano Materials**

When it comes to nanomaterials, we usually refer to materials composed of basic units with a size of 1-100nm. This material has gradually been used in various fields of life and scientific research. Precisely because its size is between 1-100nm, which is close to the wavelength of light, nanomaterials can exhibit different characteristics from other traditional materials under the same conditions.

Nanomaterials have a large surface area, which can make them a good carrier. In addition, nanomaterials can achieve precise targeting of tumor cells, which is also one of the reasons why it is now called a hot spot in contemporary drug systems.

#### **1.3.2 The Status of Nanomaterials**

In recent years, radiotherapy or chemotherapy usually brings greater toxic side effects to patients. The selectivity of chemotherapeutic drugs is poor. It kills a large number of normal cells in human tissues while killing tumor cells, leading to the destruction of the human immune system. However, due to the relatively poor biocompatibility of the drugs, the drugs will be damaged. The utilization rate is greatly reduced.

Nanomaterials can be used to enhance traditional tumor treatments, and it can also be used a larger surface area as a chemotherapeutic drug carrier to achieve precise targeted therapy. The role of nano-medicine carriers in tumor treatment and surgery can be divided into two aspects: On the one hand, nano-materials are used as therapeutic drugs. One the another hand, nanomaterials are used as drug carriers to solve the problems of poor dispersion and high toxicity of contemporary existing drugs.

In the past ten years, the side effects of chemotherapy drugs have caused its application range to be very small. Nanomedicine applies nano-sized and nano-structured materials to the development of drugs. Its unique properties overcome the limitations of many traditional chemotherapeutic drugs and become a promising anti-cancer method.

### **1.4 The Status of Tumor Treatment Through Medicine**

The tumor not only a kind of disease, but many heterogeneous diseases characterized by rapid and uncontrolled cellular expansion as a result of genetic and epigenetic alterations, and it annually affects millions of people worldwide.<sup>[28]</sup>

Current cancer treatments include surgery, radiation therapy, chemotherapy and immunotherapy. Early diagnosis of tumors in the body can be effectively cured by surgery or radiotherapy. However, for patients with tumors that cannot be removed or received radiotherapy or have metastasized, the only available treatment options are chemotherapy and immunotherapy.<sup>[29]</sup>

At present, my country's tumor drug treatment market is dominated by chemotherapy drugs. According to the article "A Glimpse of the Domestic Cancer Drug Treatment Market" in 2019, chemotherapy drugs accounted for 73% of my country's tumor drug treatment market, of which targeted drugs and immunotherapy drugs accounted for 23% and 4%, respectively. There are several main categories of targeted drugs, namely Nimustine, Doxorubicin, Vinblastine and so on. As a traditional treatment method, the disadvantage of chemotherapy is more toxic than other treatment methods. However, targeted therapy has gradually become a hot topic in today's pharmacy system because of its clear goals, good curative effect, and less side effects. Tumor immunotherapy is considered to be the most promising method that can completely cure cancer.<sup>[30]</sup>

### **1.5 Amphiphilic Block Copolymers**

Block copolymer refers to the presence of two or more different structural segments in a single linear molecule, and copolymers with specific chemical structures and molecular weights can be synthesized as needed. Amphiphilic block copolymers can self-assemble into specific supramolecular ordered aggregates in solution, called micelles.

The amphiphilic block copolymer micelles can be loaded with a variety of insoluble anti-tumor drugs, such as tamoxifen, paclitaxel, camptothecin, vinblastine and so on. Because the blood vessels at the tumor site have high permeability and high retention, and the particle size of the polymer micelles is relatively small, it is conducive to the retention and accumulation of polymers at the tumor site. This has become one of the important hotspots of contemporary drug research system research.

Amphiphilic block polymer micelles refer to a type of core-shell structure formed by "self-assembly" of block polymers with amphiphilic structure in aqueous solution, with a hydrophobic group as the core and a hydrophilic group as the outer shell. Molecular aggregates, in this way, the hydrophilic molecules in the outer layer of the micelle can protect the hydrophobic molecules inside. Applying this phenomenon to the chemotherapy environment can protect the internal drugs under polar conditions and prevent drug degradation.

Amphiphilic block polymer micelles are used to make poorly soluble anti-tumor drug carriers, which can solubilize drugs, prolong the half-life of drugs and improve the targeting of tumor cells. It has become a research on poorly soluble antitumor drugs, and the key to the drug delivery system.<sup>[31]</sup>

## **1.6 characterizing methods**

### 1.6.1 NMR spectrum

An overview of chemical shifts: A magnetic nucleus, under the action of an external magnetic field, undergoes spin energy level splitting and energy level transitions. In organic compounds, atoms with different positions and structures will show different absorption peaks.

Nuclear magnetic resonance spectroscopy (Nuclear Magnetic Resonance Spectroscopy, NMR) NMR is to study the absorption of radio-frequency radiation (Radio-frequency Radiation) by atomic nuclei. It is the most powerful tool for qualitative analysis of the composition and structure of various organic and inorganic substances. One is to analyze the structure of chemical substances against the spectra.

### 1.6.2 IR Spectrum

Infrared spectroscopy is one of the four common spectra that can be used to determine molecular structure. The generation of infrared absorption spectrum is conditional, that is, there is a coupling effect between infrared light and molecules. In order to meet this condition, the dipole moment of a molecule must change when it vibrates, so as to ensure that the energy of infrared light can be transferred to the molecule. This energy transfer is produced by the dipole moment of the molecular vibration.

The number of infrared absorption peaks of most compounds is much smaller than the theoretical calculation of the degree of freedom of vibration. The reasons are: vibration without dipole moment change does not produce infrared absorption; absorption is degenerate; absorption falls outside the detection range of the instrument; instrument resolution is low, and the spectrum peak overlap, etc.

The intensity of infrared absorption is related to the size of the transition probability and the change of the vibration dipole moment. The greater the transition probability and the greater the vibration dipole moment, the greater the absorption intensity.

### 1.6.3 UV Spectrum

Quantitative analysis using ultraviolet-visible absorption spectroscopy can be traced back to ancient history. In 60 AD, ancient Greece had known to use schisandra infusion to estimate the iron content in vinegar. This ancient method uses human eyes to monitor, so it is also called colorimetry. In the 16th and 17th centuries, relevant analytical theories began to form a system. In 1852, Beer referred to articles published by Bouguer in 1729 and Lambert in 1760, and proposed the basic law of spectrophotometry, that is, when the thickness of the liquid layer is equal, the strength of the color is proportional to the concentration of the solution itself, thus laying the theoretical foundation of spectrophotometry, which is the famous Lambert Beer's law. <sup>[32]</sup>

It is usually caused by the transition of valence electrons after molecules or ions absorb ultraviolet or visible light. By observing the maximum absorption peak position of the ultraviolet-visible spectrum, the characteristic absorption of the compound in the ultraviolet-visible spectrum can be understood.

### 1.6.4 Tyndall Effect

John Tyndall, a British physicist, was a student of the famous scientist Faraday. He discovered the Tyndall effect in 1869<sup>[33][34]</sup>, and was the first scientist who explained why the sky is blue. Tyndall effect is the phenomenon of light scattering (also known as opalescence). Since colloidal particles scatter light to form a light path, this phenomenon is called Tyndall effect. Tyndall effect is a common physical method to distinguish colloids and solutions.

For this experiment, if the micelle solution with Tyndall effect can be successfully synthesized, it is proved to a certain extent that the synthesized polymer has colloidal properties, and further experiments can be used to verify whether the polymer is in the category of nanomaterials.

#### 1.6.5 Fluorescence spectrum

Objects are exposed to shorter-wavelength light to store energy, and then slowly emit longer-wavelength light. The emitted light is called fluorescence. If the energy-wavelength relationship diagram of fluorescence is made, this relationship diagram is the fluorescence spectrum. Fluorescence spectrum can only be obtained by spectral detection.

Through the detection of a fluorescence spectrometer, information on the excitation spectrum, emission spectrum, quantum yield, fluorescence intensity, fluorescence lifetime, Stokes shift, fluorescence polarization and depolarization characteristics, and fluorescence quenching of the substance can be obtained. Fluorescence spectrometers are widely used in the fields of chemistry, environment and biochemistry. <sup>[35]</sup>

#### 1.6.6 Particle size and DLS

DLS is the abbreviation of Dynamic Light Scattering. Dynamic light scattering technology, is a means of particle size characterization. Dynamic light scattering, also known as photon correlation spectroscopy or quasi-elastic light scattering, is a physical characterization method used to measure the particle size distribution in a solution or suspension. It can also be used to measure complex fluids such as concentrated polymer solutions. behavior. It can be used to measure the fluctuation of light intensity over time in the experiment.

The particle size distribution chart shows the proportion of particles of different diameters in the total solution. Different dispersant, the concentration will show different particle size distribution. In order to ensure that the particle diameter can be accurately obtained, generally multiple sets of measurements are taken to average.

### **1.7 The Main Purpose and Meaning of the Research**

In this paper, experiments are carried out on the synthesis of amphiphilic co-block nano-polymers with AIE characteristics, and the samples and methods made are of great research significance for current drug delivery systems. It is particularly helpful for the

current nanomedicine to be used in the field of tumor treatment. In this case, patient may not be struggle from the pain of traditional medicine treatment by-effect. Also, with the target character and aggregation-included condition, the medicine could easily transfer to the aim cells or the areas. As a kind of amphiphilic copolymer carrier, different surface has different function means to different substance. The structure of the polymer is hydrophilic on one side and hydrophobic on the other side. On the one hand, it helps to protect the drug from being decomposed or destroyed by other fluids in the body, and on the other side, it can be transported and flowed well in the body.

Fluorescence imaging technology can be used in the medical field as a method and means for cancer diagnosis. Due to the fluorescence characteristics caused by a certain number of accumulations, AIE materials have high biological imaging capabilities, and because such materials generally have high stability. Therefore, AIE materials have a certain future and greater competitiveness in the use of materials in any field and aspect in the future with their character.

The high-efficiency catalytic performance, super-hydrophobicity and other characteristics of nanomaterials can realize the high-efficiency utilization of drugs, which is of great significance to drug-carrying systems today and in the future. Since most drugs have poor hydrophilicity, if the drugs are wrapped in amphiphilic materials and aggregated and released at designated locations, the utilization rate of the drugs can be greatly improved and the waste of drugs can be reduced.

## Chapter 2. Experiment Section

### 2.1 experiment medicine and instrument

Reagent	Specifications	Manufacturer
Dichloromethane	AR	Fuyu Chemical
Boron tribromide	99.90%	Energy Chemical
N-butyl lithium	15%	Aladdin
Methane	AR	Fuyu Chemical
Ethyl ether	AR	Yantai Far East Fine
Polylactide	AR	Aladdin
Tetrahydrofuran	AR	Tianjin Kemiou Chemical Reagent Co., Ltd
Dimethyl sulfoxide	AR	Fuyu Chemical
Chloroform-d	D 99.8%+0.03% TMS	Tenglong Weibo
Sodium hydrogen phosphate dodecahydrate	AR	Sinopharm Chemical Reagent Co., Ltd
Disodium hydrogen phosphate dihydrate	AR	Macklin
Cyclobutane tetraformic acid dianhydride	98%	Energy Chemical
1-(3- dimethylaminopropyl)-3- ethylcarbodiimine hydrochloride	98%	Aladdin
N-hydroxysuccinimide	98%	Aladdin
Triethylamine	99.50%	Aladdin
Para-toluene sulfonic acid hydrate	AR	Aladdin
Toluene	AR	Yantai Far East Fine Chemical CO., LTD
4-methoxy benzophenone	98.00%	Aladdin
Ammonia	25%-28%	Laiyang Kant Chemical Co., Ltd
Para-toluene sulfonyl chloride	AR	Aladdin
Hydrochloric acid	AR	Leyan
Magnesium sulfate(s)	AR	Sinopharm

Instrument	Type	Manufacturer
Intelligent magnetic agitator	ZnCl-BS140*140	Gongyi Yuhua Instrument Co., Ltd
Electronic balance	QUINTIX224-1CN	Sartorius
Vacuum drying oven	DZF-6216	Shanghai Yiheng Scientific Instrument Co., Ltd.
Two-value capacitor asynchronous motor	YL71240	Shaoxing Wanpeng Electromechanical Co., Ltd.
UV-visible spectrophotometer	UV2800S	Shanghai Sunny Hengping Scientific Instrument Co., Ltd.
Fluorescence spectrophotometer	F97pro	Lengguang Technology
Ultrasonic signal generator/ultrasonic probe	Joyn-1000D	Shanghai Joyn Electronic CO., Ltd.
Heat-collecting thermostatic magnetic stirrer	DF-101S	Gongyi Yingyu High-tech Instrument Factory
Laser particle size analyzer	Mastersize 2000	Malvern

## 2.2 Synthetic Bismethoxytetraphenylethylene (MeO-TPE-OMe)

Weigh 9g zinc powder and 9g methoxybenzophenone as reactants, add about 150ml of anhydrous tetrahydrofuran (THF) into a 500ml two-necked flask, and then ventilate with nitrogen to ensure inert gas conditions during the whole reaction. Add zinc powder and stir in an ice water bath. Using a clean, with inert gas-changed needle tube, add 66 mL of titanium tetrachloride (TiCl<sub>4</sub>) in dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>) solution from the top of the constant pressure funnel, with a concentration of 1 mol/L.

After reacting for 0.5h, it was transferred to an oil bath at a temperature of 75°C, and refluxed for 24h by condensing.

When the reaction was stopped, the temperature needs to be lowered to room temperature, and 10 mL of saturated K<sub>2</sub>CO<sub>3</sub> solution was added with stirring. When the

reaction was stopped, the bubbles appeared, and the reaction was started to be terminated. Add 100 mL of anhydrous  $\text{CH}_2\text{Cl}_2$ , stir for 0.5h, and freeze for 3.5h.

Add 2cm thick diatomaceous earth into the Buchner funnel. Before suction filtration, add  $\text{CH}_2\text{Cl}_2$  solution to soak the filter paper. After filtration, it was a light green-yellow solution.

The sample was filtered and rotary evaporated into a dry solid, and the sample was collected for next step. Weigh 4 g of the product into a 250 mL round-bottom flask, add a certain amount of magnets, and pour 0.4 g of p-toluene sulfonic acid hydrate into the flask. Use a cold trap to ventilate the device. When ensuring the device is in the inert gas condition, set the oil bath temperature to  $140^\circ\text{C}$  and react for 24 hours. After the reaction is completed, use a beaker to catch the liquid in the oil-water separator, but still remain a constant level of liquid when taking out the liquid to prevent air from entering the system.

Add appropriate amount of magnesium sulfate to dry the sample. When the added magnesium sulfate is no longer lumpy, but looks like in the form of floating powder, it means that the amount of magnesium sulfate is sufficient. The drying time is half an hour. Suction filtration, rotary steaming, and finally a tan fluid is obtained. Add a small amount of petroleum ether (as a non-benign solvent) to the fluid and perform rotary evaporation. Ultrasound the sample after rotary evaporation to obtain a solid sample, and then add a small amount of dichloromethane to dissolve the sample and stir it into a sticky liquid. Suction the solid, dissolve the sample with about 50ml of dichloromethane, add 14 spoons of 100-200 mesh silica gel powder for rotary steaming until the sample is dry powder.

Purified the sample. Before filling the column, add about 25cm high 300-400 mesh silica gel powder, use a pump to solidify, add petroleum ether to infiltrate, after the petroleum ether drops below the column belly, add the product dry powder, try to ensure the sample filling smoothly and balance. Add a buffer solution which is made of petroleum ether and 300-400 mesh silica gel, add absorbent cotton to balance the liquid, in case the products wasting during the purified process, and then add 500 mL of petroleum ether.

When starting to screen the sample through the column, first use a larger ratio of dichloromethane and petroleum ether (1:6) as the developing agent, and use a capillary tube and a UV lamp to observe the outflow of the sample and impurities. When weak fluorescence appears in the solution, the proportion of the developing agent can be reduced to ensure the purity of the collected sample.

When all the sample is collected, use rotary evaporator to remove the liquid. Add petroleum ether into the solid which gotten from the rotary evaporator. Solids are dissolved by ultrasonic waves, freezing and drying. Finally put it into the freezer to wait for another experiment.

### **2.3 Synthesis Bishydroxytetraphenylethylene (HO-TPE-OH)**

Prepare the bismethoxytetraphenylethylene prepared in 2.1, put it into a two-necked flask, and add 20-30 mL of anhydrous dichloromethane to the two-necked flask. Operate in an ice-water bath again, perform one air exchange, add about 13mL of boron tribromide to the needle tube, and exchange air twice. After keeping the device and ensuring that it is sealed for 1 h, remove the ice-water bath, inert gas balloon and cold trap, and react at room temperature for 16 h.

After 16 hours of reaction, in a fume hood, while stirring, 20 mL of methanol was slowly added dropwise to terminate the reaction. Transfer the solution to a separatory funnel, add 300 mL of dichloromethane to dissolve, and wash with about 20 mL of saturated sodium chloride solution. After washing and standing for stratification, the inorganic phase was transferred to a beaker containing 300 mL of ice distilled water, and the organic phase was subjected to rotary evaporation.

The solid after rotary evaporation was obtained, which was dissolved in 20 mL of methanol, and the dissolved solution was added dropwise to the inorganic phase to produce a flocculent white precipitate. Use a sand core funnel for suction filtration to collect the filtered solids. The obtained solid is dissolved in dichloromethane, and an appropriate amount of magnesium sulfate is added to dry for 0.5h (the amount of magnesium sulfate is

the same as the amount of magnesium sulfate in step 2.1). After drying, use a funnel to filter with suction, and spin-evaporate the filtrate to obtain bishydroxytetramethylethylene.

#### 2.4 Synthesis PEG<sub>2K</sub>-NH<sub>2</sub>

Prepare hydroxy polyethylene glycol with a molecular weight of 1900 and a certain amount of 4-toluenesulfonyl chloride. Add magnets to a two-necked flask, add 10g of mPEG<sub>1900</sub>, and stir to dissolve with 100-200ml of dichloromethane. In an ice water bath, add 9.533 g of 4-toluenesulfonyl chloride, and inject nitrogen gas with a needle to ensure that the reaction proceeds under inert conditions. Use a needle tube to add triethylamine drop by drop, continue to fill with nitrogen for 5 minutes, and then pull out the needle. Use a sealing film to ensure the sealing of the experimental equipment, react for 72 hours under the conditions of dark and room temperature.

During the reaction, the solution changed from a clear transparent solution to a light gray transparent solution.

After the reaction, the solution was poured into a separatory funnel and washed three times with 60 mL of dilute hydrochloric acid, and then washed three times with saturated sodium chloride solution. After drying with anhydrous magnesium sulfate for 0.5 h, the solution was revolved to 15 mL. Settling with 300mL ice ether, after settling, put it in the refrigerator overnight. The solid was filtered the next day, and the filtered solid was vacuum dried for 24 hours.

The solid was dissolved in saturated ammonia water, ventilated, protected from light, and stirred at room temperature for 5-6 days.

After the reaction, it was extracted with dichloromethane solution, 120 mL each time, 4 times in total. In the liquid separation operation, the organic phase is on the bottom and the inorganic phase is on the top. Rotate the lower organic phase solution to 15 mL. The solution after rotary evaporation was settled into petroleum ether under ultrasonic conditions. Put the settled solution in a refrigerator overnight, remove the petroleum ether

part the next day, and dry the solid in vacuum to obtain an amino polyethylene glycol sample.

### **2.5 Synthesis HO-TPE-OH-CBDA-mPEG<sub>2k</sub>-NH<sub>2</sub> Polymer**

Prepare a clean polymerization bottle, add 0.2g CBDA and 0.488g HO-TPE-OH into the polymerization bottle, ventilate three times, and inject 5 mL of dewatered DMSO solution with a syringe. The reaction was stirred for 48h at 60°C and protected from light, and then cooled to room temperature after the reaction. Add EDC and NHS to ventilate 3 times, stir and react for 1-2h at room temperature and protected from light. Then, 5 mL of DMSO was used to dissolve the amino polyethylene glycol, and the dissolved mixed solution was injected into the polymerization bottle with a needle, and the reaction was continued at room temperature for 48 hours.

After the reaction, the DMSO solution was drained under reduced pressure, the DMSO that could not be drained was dialyzed with ultrapure water, and the dialysis solution was lyophilized into powder.

Finally, the obtained polymer was subjected to a series of characterization and analysis.

## Chapter 3. Results and Analysis

Characterization and analysis of the synthesized HO-TPE-OH monomer and TPE-CBDA-PEG polymer.

The synthesis step diagram is as follows:

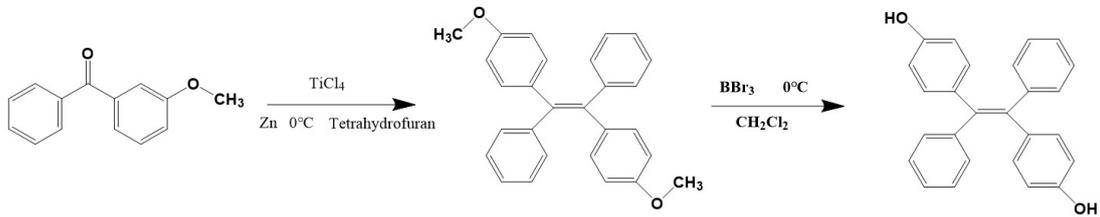


Figure 1. Synthesis of HO-TPE-OH

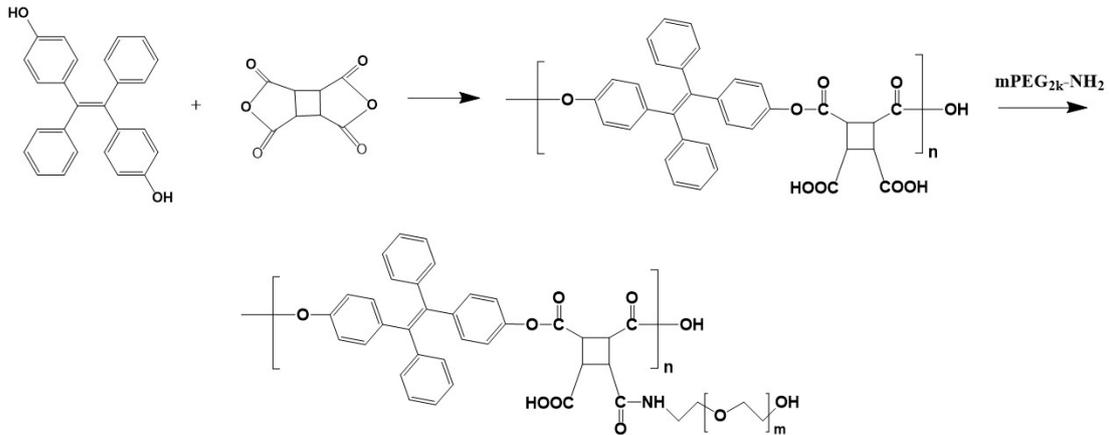


Figure 2. Synthesis of TPE-CBDA-PEG<sub>2k</sub>

### 3.1 Analysis of HO-TPE-OH Sample

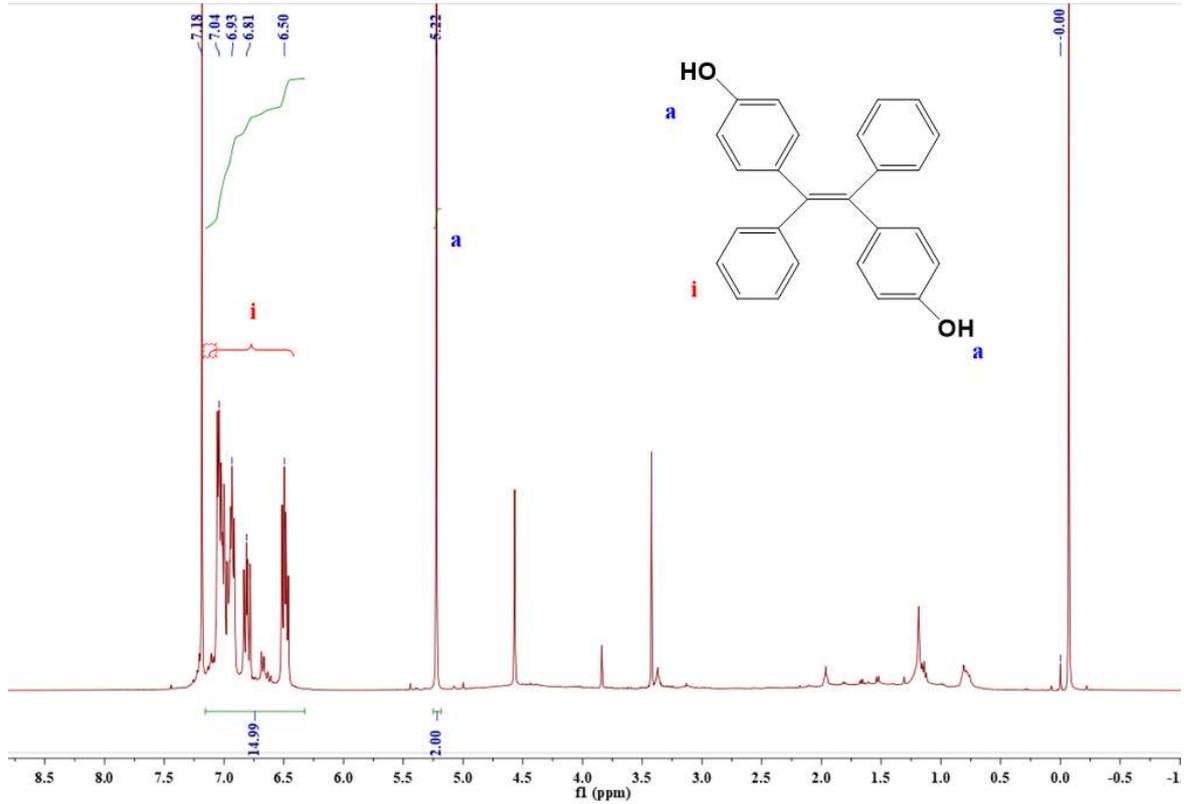


Figure 3. NMR Spectroscopy and Structural Formula of HO-TPE-OH

The structure of the monomer is analyzed by NMR spectroscopy. It can ensure that the polymer synthesized later has a certain degree of purity. It can be known from the NMR spectrum that the sample obtained is HO-TPE-OH. Other unmarked peaks may be impurity peaks, so do not do too much analysis. The peak around 1.18ppm is the peak of water, so no analysis is needed.

### 3.2 Analysis of HO-TPE-OH-CBDA-mPEG<sub>2k</sub>-NH<sub>2</sub> Polymer

The synthesized polymer was analyzed by nuclear magnetic spectroscopy for its structural composition.

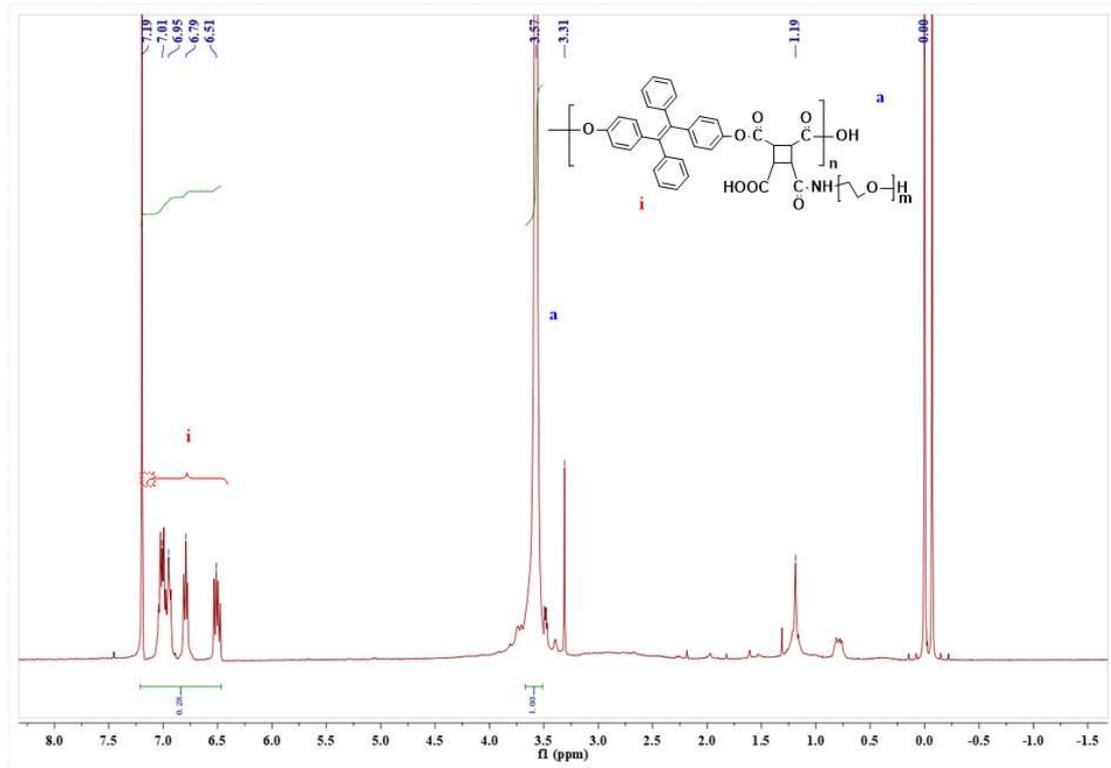


Figure 3. Structural Formula and NMR Spectrum of TPE-CBDA-PEG

The peaks that mainly exist and can be found in the figure are the peaks of the benzene ring and the hydroxyl group. Other unmarked peaks may be impurity peaks, so do not do too much analysis. There should be a water peak around 1.18 ppm, so no analysis is needed.

It can be seen from the spectrum that the polymer has been successfully synthesized and can be used for the next step of characterization.

Analyze the particle size of the polymer to observe the stability of the drug under different pH conditions. Because PH=7.4 belongs to a good neutral environment, and the acidic environment of PH=5.0 is close to the environment in the human body.

40 mg of polymer was dissolved in 2 mL of THF, dissolving for 6 hours. Then use an organic filter to drop the solution into 38 mL of filtered PB7.4 solution to form micelles. Use a dialysis bag to perform dialysis for 3 hours, then change the water every 0.5 hours during this period to ensure that all solvents are precipitated. Divide the dialysis solution

into two equal parts, of which 20 mL is regarded as PB=7.4, and the other 20 mL is added with 0.1 mol/mL dilute hydrochloric acid to adjust Ph, which is regarded as PB=5.0.

In order to carry out a blank control test, at the same time weigh 20 mg of polymer and dissolve it in 1 mL of THF, dissolve it for six hours, and then filter it with a new organic filter. The filtered solution is dissolved in 19 mL of clean ultrapure water. During dialysis with a 3500 model dialysis bag for three hours, the dialysis water was changed every half an hour during this period to ensure that all the tetrahydrofuran was precipitated. The obtained micelles were tested for particle size, and the results obtained were compared with PB5.0 and PB7.4.

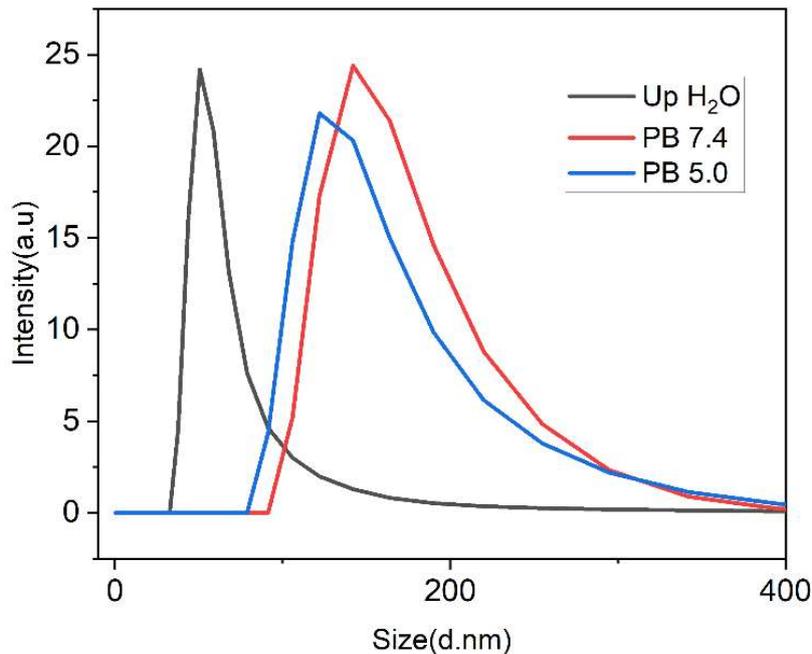


Figure 4. Different Size in Different pH condition

Under different acid and base conditions, the particle size of the polymer will also change, and the particle size of the polymer in ultrapure water is relatively small.

According to the particle size diagram, it can be inferred that the polymer has a certain degree of hydrophilicity and can exhibit good colloidal properties in a pure water environment. For the adjusted pH, the diameter of the polymer micelles will slightly change. It is large, but still has certain colloidal properties, which proves that the nano-medicine has certain stability.

The first measured time is recorded as 0h, and the polymer particle size is measured every certain time interval thereafter, totaling 24h. The following figure can be obtained.

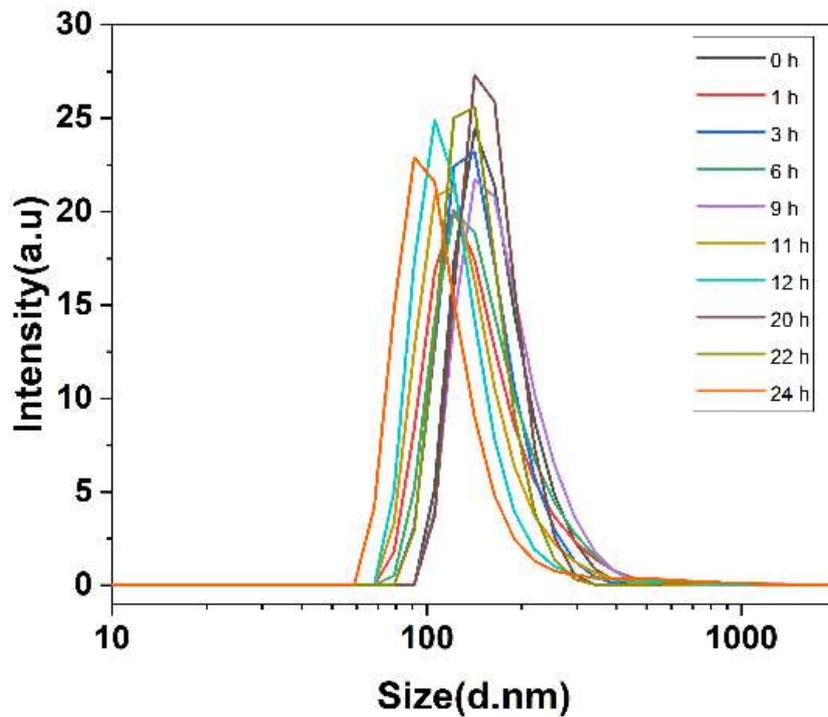


Figure 5. Stability of polymer in PB=7.4 solution

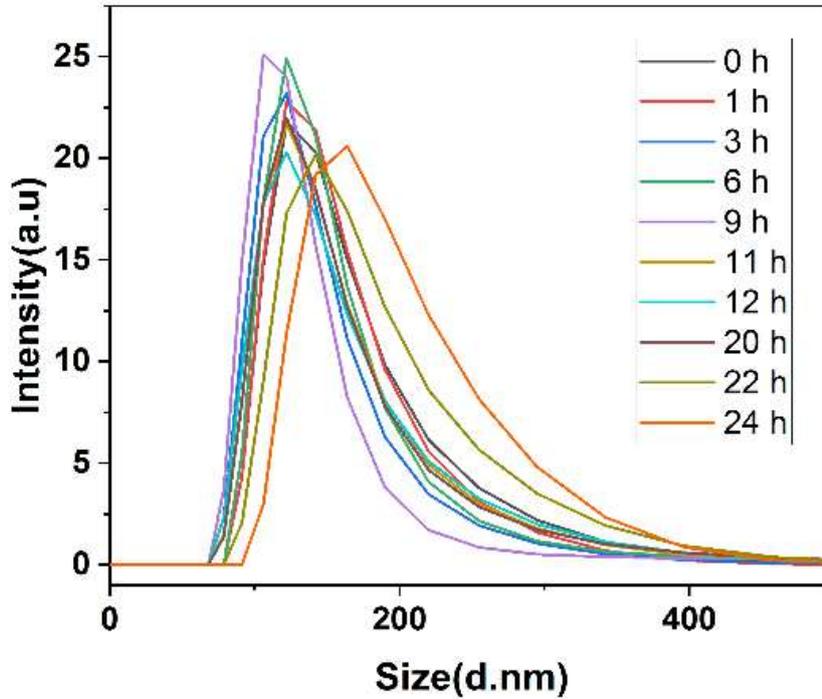


Figure 6. Stability of polymer in PB=5.0 solution

It can be seen that the synthesized polymer has a certain good stability under different pH. Compared with the neutral condition, the particle size of the polymer under the acidic condition is slightly higher than that under the neutral condition.

When testing the Tyndall effect of the polymer, dissolve 10 mg of the sample in 1 mL of THF. After dissolving for 6 hours, use an organic filter to drop the solution into 9 mL of the filtered PB7.4 solution. Dialysis for 3h, during which the water was changed every 0.5h to ensure that the solvent was completely precipitated. Transfer the dialysis solution to a clean four-way cuvette and measure the tyndall effect. A path of light can be found, which proves that the dissolution system of the prepared polymer is a colloid, which is also in line with the properties of nanomaterials.

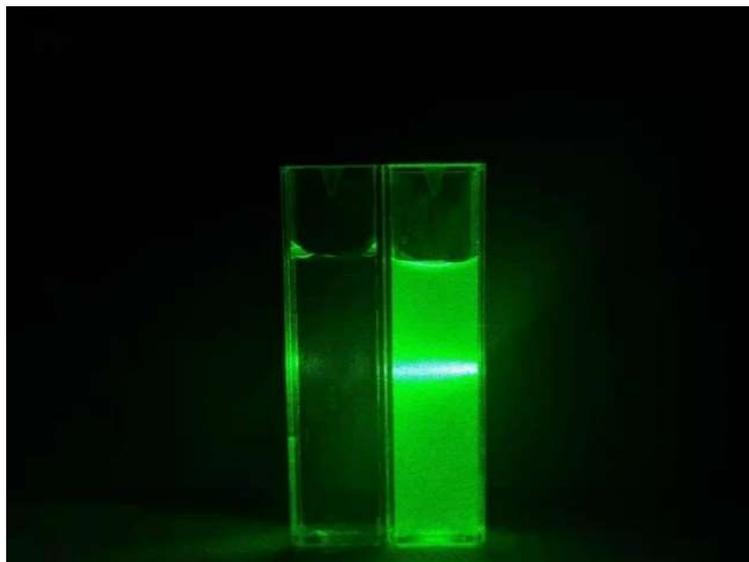


Figure 7. Tyndall effect of polymer (the light in the picture shows the path of light through the polymer colloid, but there is no light in the water)

The character has been showed on the picture, which the polymer micellar gives the light road but the water does not. Compared with previous related theories, it can be concluded that the prepared polymer micelles belong to the category of nano-material particles.

For sample preparation, weigh 100mg of polymer, add it to a beaker containing ultrapure water (concentration 1mg/mL), first sonicate at ordinary power for 10 minutes, then use high-power sonication for 5 minutes, then transfer to a brown volumetric flask for constant volume, continue ultrasound the samples for 20 minutes, which is sample 1. Prepare a series of volumetric flasks, and dilute sample 1 in multiples to obtain a series of samples, which are marked as 2/3...6/7. In order to ensure the uniformity of the sample, the first few samples with high concentration must be sonicated for 10 minutes before each configuration.

According to the concentration from small to large, measure the ultraviolet absorption spectrum and the fluorescence absorption spectrum respectively.

Adjust the wavelength and measure the ultraviolet absorption spectrum. It can be seen that the best absorption wavelength is about 340nm.

According to the ultraviolet spectrum, the best excitation wavelength of the polymer is around 360 nm. The following figure can be obtained by using the emission mode to perform fluorescence tests on polymer solutions of different concentrations. It can be seen the maximum absorption wavelength of the polymer should be in the blue region of 450 nm.

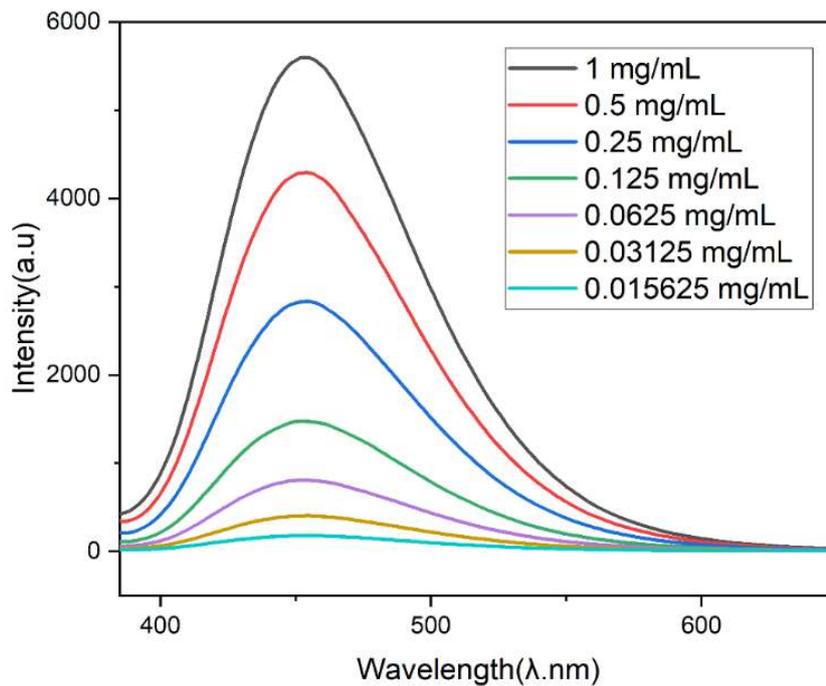


Figure 8. Fluorescence spectra of different concentrations of polymers under the same emission intensity

According to the fluorescence spectrum, it shows the concentration of polymer becomes weaker, the intensity of fluorescence becomes correspondingly lower. This is consistent with the fact that the aggregated state of AIE materials emits high-intensity fluorescence, and the fluorescence intensity becomes weaker in the low-concentration state.

After that, the samples of different concentrations were photographed under 365nm ultraviolet light. The main purpose of this step is to observe whether AIE phenomenon occurs in polymer micelles. If the synthesized polymer emits stronger fluorescence as the concentration increases, and the fluorescence effect becomes weaker when the concentration decreases, then it can be proved that the synthesized polymer has the characteristics of AIE materials, which meets the initial experimental expectations, and can be used in practical applications.



Figure 9. The greater the concentration of the solution under the UV lamp, the stronger the fluorescence intensity

According to the concentration from large to small, after rowing from left to right once, according to the above figure, you can easily get the following information: polymer micelles will fluoresce under the irradiation of ultraviolet lamps, indicating that the polymer has a certain fluorescence effect. Moreover, as the concentration continues to deepen, the fluorescence effect of polymer micelles becomes stronger and stronger; as the concentration decreases, the fluorescence effect of polymer micelles continues to weaken. It can be explained to a certain extent that the synthesized polymer has the AIE effect and the reaction to light is more obvious.

In order to get much further information to deeper understand the synthesized polymer, the characteristic functional groups, such as hydrophilic hydroxyl groups, it could be seen intuitively through the infrared spectrum. According to the related literature and data from the library, the position of the hydroxyl group is probably between  $2800\text{-}3500\text{ cm}^{-1}$ , and for

the anhydrides located at  $1740\text{-}1780\text{ cm}^{-1}$ , carbon-carbon double bond peak is between  $1695\text{-}1540\text{ cm}^{-1}$ . The whole IR spectrum of the polymer showed below:

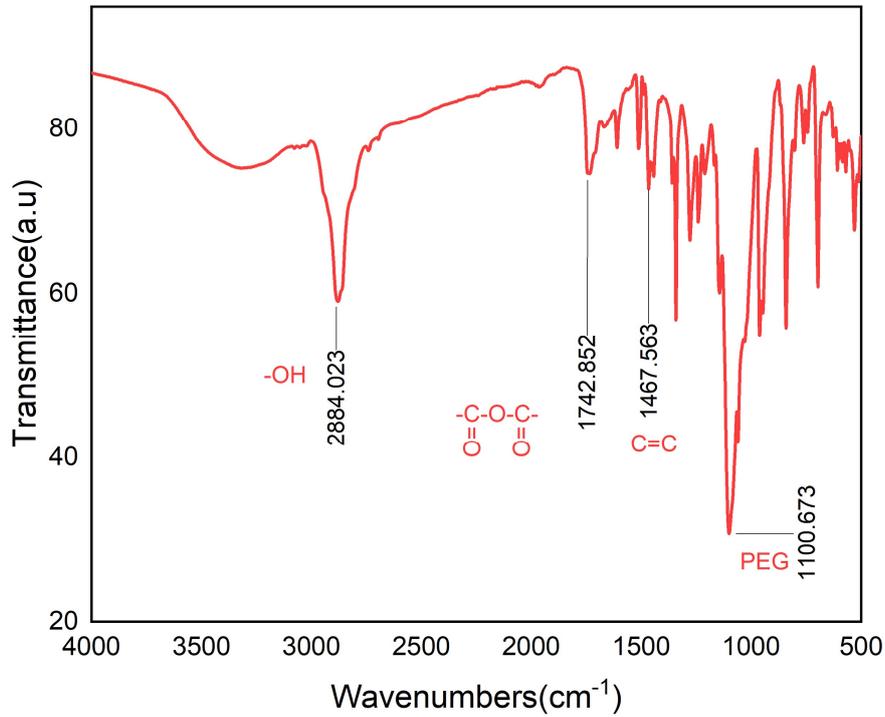


Figure 10. Infrared spectra of polymers

According to the data obtained and the data in the literature for reference, the functional groups are shown in the infrared spectrum, and then calculate the functional groups contained in the polymer, which can prove that the polymer containing the relevant functional groups has been successfully synthesized.

As the spectrum shows, there is a single peak at  $2884\text{ cm}^{-1}$ , which means there are hydroxyl group in the polymer. The experiment process truly combined the hydroxyl group into the polymer. In this case, we could accurately realize the hydroxyl in the synthesis polymer.

And in the entire spectrum, no obvious impurity peaks appeared, indicating that the synthesized polymer not only has a corresponding structure, but also has good purity.

## Chapter 4. Conclusion

After a series of synthesis and processing, this experiment successfully synthesized an amphiphilic nano drug carrier with aggregation-induced luminescence effect, and carried out related systematic characterization. Experiments continue to modify the material and finally prove that the synthesized nanocarrier has AIE characteristics and meets the standards of nanomaterials. Drugs with aggregation-induced luminescence effects can help today's tumor drug systems to complete efficient and targeted treatments. Judging from various data sheets and figures, the synthesis of the polymer meets the expected design.

Of course, this experiment and thesis still have a lot of points worthy of improvement, as well as deficiencies and remaining problems. For example, whether the drug is actually used in biological practice can still achieve the expected effect in the experiment, and it is not known whether the organism will reject the carrier. In the experiment, there may be fluorescence quenching caused by unavoidable strong light factors, which will reduce the sensitivity of the sample and the effect will be worse. This is also one of the problems that need to be changed later. After all, the reflected environment of the experimental simulation is not particularly rigorous, and there are certain ideal conditions and conditions. In this regard, it should be possible to find information from other authors' literature, which can be helpful for subsequent experiments and applications.

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Now I have so many feelings, it is better to seal it with this article. I believe, life is a Mobius ring, all ends are also the beginnings.