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# The synthesis of PEG-PCL and the physicochemical properties of its self-assembled nanoparticles

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In this paper, poly(caprolactone)-poly(ethylene glycol) (PEG-PCL) was synthesized by using potassium bis(trimethylsilyl)amide as a catalyst, ethylene oxide and ε-caprolactone as a raw material. Then, amphiphilic block polymers PEG-PCL of different molecular weights were synthesized by this method. These were PEG2K-PCL2K, PEG5K-PCL2K and PEG5K-PCL5K. But this method is different from most literature reports, where the amphiphilic block copolymer PEG-PCL was synthesized by using fixed molecular weight polyethylene glycolmonomethyl ether (PEG) and ε-caprolactone as raw materials, and stannous caprylate ($Sn(Oct)_2$) as a catalyst. This paper introduces the detailed experimental procedures. The copolymers obtained were characterized by Fourier-transform infrared spectroscopy, gel permeation chromatography and hydrogen nuclear magnetic resonance. Using the method of dialysis, the amphiphilic blockcopolymer PEG-PCL was self-assembled in water to form polymer nanoparticles. The physicochemical properties of the polymer nanoparticles were characterized by dynamic laser scattering, scanning electron microscopy and Zeta potentiometer.

**Keywords**: PEG-PCL, nanoparticles, amphiphilic block copolymer, self-assembled nanoparticles.

Поли(капролактон)-поли(этиленгликоль) (PEG-PCL) синтезирован с использованием бис(триметилсилил)амида калия в качестве катализатора, оксида этилена и ε-капролактона как сырье. Синтезированы амфифильные блочные полимеры PEG-PCL различной молекулярной массы: PEG2K-PCL2K, PEG5K-PCL2K и PEG5K-PCL5K. Метод отличается от большинства литературных данных, в которых амфифильные блок-сополимеры PEG-PCL синтезированы используя полиэтиленгликольмонометиловый эфир с фиксированной молекулярной массой PEG и ε-капролактон в качестве сырья, каприлат олова $Sn(Oct)_2$ в качестве катализатора. Полученные сополимеры охарактеризованы с помощью инфракрасной спектроскопии с Фурье-преобразованием, гель-проникающей хроматографии и водородного ядерного магнитного резонанса. Используя метод диализа, амфифильный блок-сополимер PEG-PCL самособирался в воде с образованием наночастиц полимера. Физико-химические свойства полимерных наночастиц характеризовались динамическим лазерным рассеянием DLS, сканирующей электронной микроскопией SEM и дзета-потенциометром.

**Синтез ПЕГ-ПКЛ і фізико-хімічні властивості його самоорганізованих наночастинок**. *Fawu Wang, Zhongxin Zhang, Huaxin Rao.*

Полі(капролактону)-полі(етиленгліколь) (PEG-PCL) синтезувано з використанням біс (триметилсиліл)аміду калію в якості каталізатора, оксиду етилену і ε-капролактону як сировини. Синтезовано амфіфільні блокові полімери PEG-PCL різної молекулярної маси: PEG2K-PCL2K, PEG5K-PCL2K і PEG5K-PCL5K. Метод відрізняється від більшості літературних даних, в яких амфіфільні блок-сополімери PEG-PCL синтезува-

но, використовуючи поліетиленглікольмонометиловий ефір з фіксованою молекулярною масою PEG і ε-капролактону в якості сировини, каприлат олова ($Sn(Oct)_2$) в якості каталізатора. Отримані сополімери охарактеризовано за допомогою інфрачервоної спектроскопії з Фур'є-перетворенням, гель-проникаючої хроматографії і водневого ядерного магнітного резонансу. Використовуючи метод діалізу, амфіфільний блок-сополімер PEG-PCL самозбирається у воді з утворенням наночастинок полімеру. Фізико-хімічні властивості полімерних наночастинок характеризовано динамічним лазерним розсіюванням, скануючою електронною мікроскопією і дзета-потенціометром.

## 1. Introduction

Amphiphilic polymers due to the solubility of each segment in selective solvents can occur as a result of associating polymer micelle formation. Polymer micelle has a low critical micelle concentration at the large solubilization of space, and structure stability; also, due to the different properties of a hydrophobic polymer chain segment to the physical and electrostatic interactions with drugs, has wide application prospect as a drug carrier [1]. Due to its biocompatibility and other excellent properties, poly(caprolactone) (PCL) has become in the focus of research on biological materials in recent years [2].

As a biodegradable material, polyhexolactone is non-toxic and has no side effects, but it has high crystallinity and is not easy to degrade. As drug carriers, hydrophobic PCL nanoparticles are easy to be adsorbed by proteins and recognized and captured by reticuloendothelial cells, and have a short cycle time in the body [3]. Therefore, it is necessary to conduct hydrophilic modification on the surface of the PCL nanoparticles. Polyethylene glycol (PEG) is a biocompatible non-ionic water-soluble polymer with low toxicity to humans and its properties have been recognized by the food and drug administration (FDA) of the United States [4].

So it is necessary to study amphiphilic block polymers (PEG-PCL). PEG-PCL with different molecular weight was synthesized in this paper and their physicochemical properties were analyzed [5, 6].

## 2. Experimental

### 2.1 Materials

Ethyleneoxide (AR,99 %), ε-caprolactone (AR,99 %), tetrahydrofuran (AR,99 %), calciumhydride (AR,98 %), methanol (AR,99.5 %), diethylether (AR,99 %), benzophenone (AR,99 %), natrium (AR,99 %), potassium bis (trimethylsily) amide (1.0 mol solution in THF,100 ml), potassium hydroxide (AR,99 %), acetic acid (AR,99 %).

### 2.2 Purification of materials

In the experiment, ethylene oxide and ε-caprolactone are easy to react with water molecules and external air, resulting in many impurities in the final product, which are not easy to separate. In order to get a purer polymer, the raw material needs to be purified [7].

Ethylene oxide: In the distillation device, the operations of vacuum and nitrogen were repeated three times to ensure that the system is free of water and oxygen. Calcium hydride and potassium hydroxide (mass ratio 1:1) were used as desiccant, and the fractions were collected in −10°C (ice salt bath) after distillation [8].

ε-Caprolactone: Calcium hydride was used as a desiccant and ε-caprolactone was dried for 24 h. The fractions at 90°C to 110°C were collected by vacuum distillation [9].

Tetrahydrofuran: In the presence of metallic sodium, tetrahydrofuran requires reflux for three days. Dibenzophenone was used as a color reagent, distilled until the solution is blue-purple, and then collected for later use [10].

### 2.3 Methods

The synthesis of poly(caprolactone)-poly (ethylene glycol) (PEG2K-PCL2K)

The reaction tube was drained, then, 1.77 g of ethylene oxide monomer and 10 ml of THF were added in the reaction tube. 1.7 ml of potassium bis(trimethylsilyl)amide was added as an initiator at the temperature of 40 °C with magnetic stirring at 300 rpm for 24 h. As a result, polyethylene glycol was synthesized, then it can be used as an initiator to initiate the ring-opening polymerization of ε-caprolactone. Amphiphilic block polymers (PEG2k-PCL2k) can be synthesized by this method [11, 12]. Specific steps are as follows: 1.4 ml of the ε-caprolactone monomer and 8 ml of tetrahydrofuran are dropped into the reaction tube with a syringe. In order to avoid gelation in the ring-opening polymerization of ε-caprolactone, the temperature should be around 0 °C; so, the reaction tube should be in the ice-water. The ε-caprolactone mono-

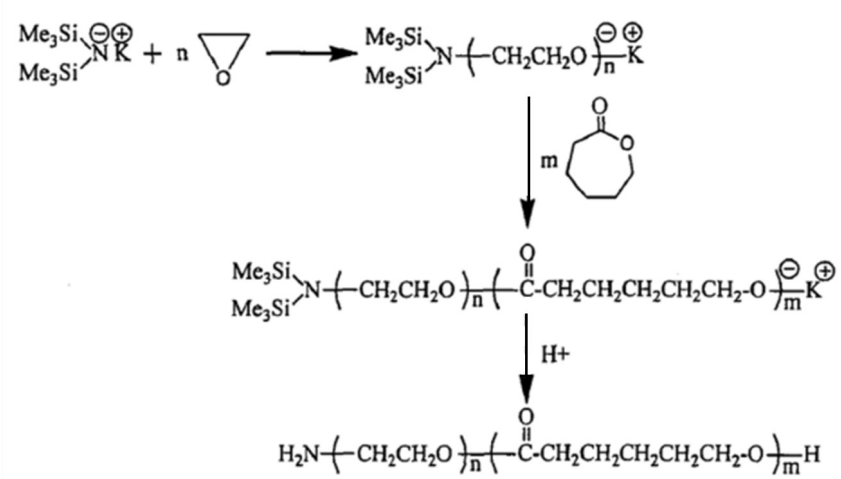

Fig. 1. Chemical equations for synthesis of poly(caprolactone)-poly(ethylene glycol)(PEG-PCL).

mer is added into the tube when the temperature is appropriate [13]. After the drip is finished, it reacts at room temperature for half an hour. Then 152 μl of acetic acid is added to terminate the reaction. The obtained polymer was precipitated into a white solid by a mixture of anhydrous methanol and anhydrous ether ($V/V$ = 1:3) [14]. Then the material was left overnight at room temperature and vacuum dried.

The synthesis of poly(caprolactone)-poly (ethylene glycol) (PEG5K-PCL2K)

Using the above method PEG5K-PCL2K was synthesized. In the step of synthesizing poly(ethylene oxide) macromolecules as initiators, 4.3 g of ethylene oxide monomer, 10 ml of tetrahydrobaran, and 1.8 ml of potassium bis(trimethylsily)amide were added to the reaction tube. 1.9 ml of the ε-caprolactone monomer and 8 ml of tetrahydrofuran were added to the reaction tube in the reaction of ring-opening polymerization of ε-caprolactone induced by high molecular polyethylene glycol. Then 148 μl of acetic acid was added into the reaction tube as a termination agent, after the reaction was completed. The obtained polymer was precipitated into a white solid by a mixture of anhydrous methanol and anhydrous ether ($V/V$ = 1:3). Then the material was left overnight at room temperature and vacuum dried. The synthesis of poly(caprolactone)-poly (ethylene glycol) (PEG5K-PCL5K)

Using the above method, PEG5k-PCL5k was synthesized. In the step of synthesizing poly(ethylene oxide) macromolecules as initiators, 4.3 g of ethylene oxide monomer, 10 ml of tetrahydrofuran, and 1.8 ml of potassium bis(trimethylsilyl) amide were added to the reaction tube. 4.2 ml of the ε-caprolactone monomer and 10 ml of tetrahydrofuran were added to the reaction tube in the reaction of ring-opening polymerization of ε-caprolactone induced by high molecular polyethylene glycol. Then 150 μl of acetic acid was added into the reaction tube as a termination agent, after the reaction was completed. The obtained polymer was precipitated into a white solid by a mixture of anhydrous methanol and anhydrous ether ($V/V$ = 1:3). Then the material was left overnight at room temperature and vacuum dried.

The reaction equation presented in Fig. 1.

## 3. Results and discussion

The copolymer was characterized by Fourier-transform infrared (FT-IR) spectroscopy, gel permeation chromatography (GPC), and hydrogen nuclear magnetic resonance ($^1$H-NMR). Then, amphiphilic block copolymers (PEG-PCL) were self-assembled in water to form polymer nanoparticles by the method of dialysis. The physicochemical properties of the polymer nanoparticles were characterized by dynamic laser scattering (DLS), scanning electron microscope (SEM) and Zeta potentiometer.

*3.1 The analysis of Fourier-transform infrared (FT-IR) spectroscopy*

As shown in Figs. 2–3, obvious peaks appear around 1730 cm$^{-1}$, this is caused by the stretching vibration of C=O in the -O-C=O group. It can be preliminarily judged that polyethylene glycol successfully initiated the ring-opening polymerization of ε-caprolactone, and the hydroxyl group of polyethylene glycol successfully connected to the aldehyde group of ε-caprolactone [15]. And in the range of 3300 cm$^{-1}$ to 3600 cm$^{-1}$,

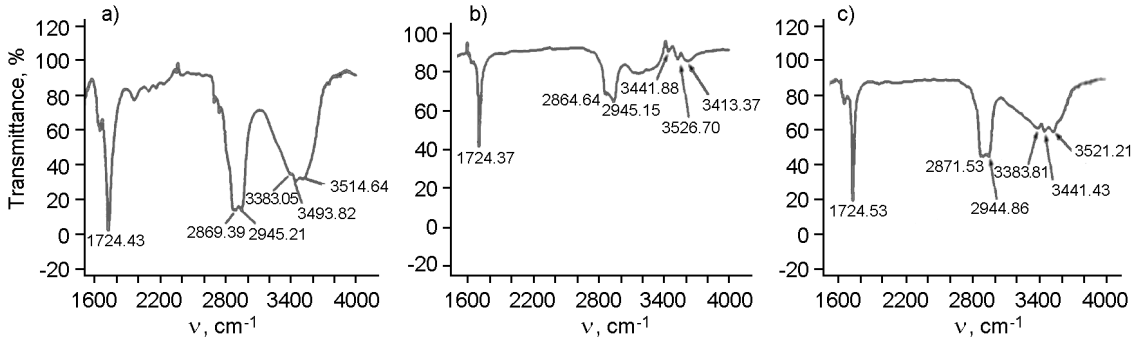


Fig. 2. Figure a, figure b and figure c are Fourier infrared spectra of polymers $PEG_{2K}$-$PCL_{2K}$, $PEG_{5K}$-$PCL_{2K}$ and $PEG_{5K}$-$PCL_{5K}$, respectively.

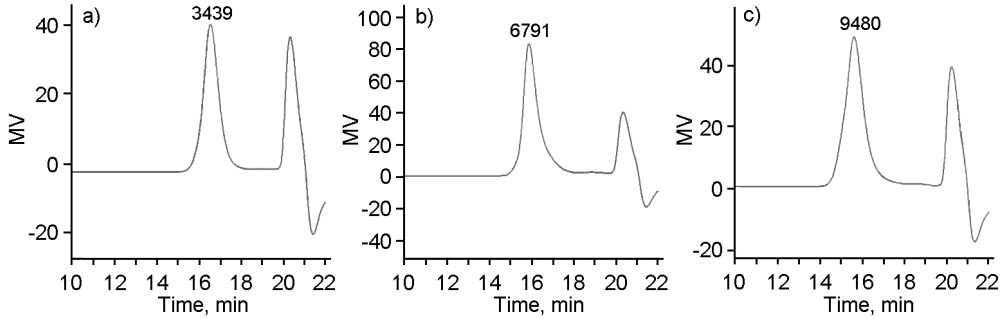


Fig. 3. Figure a, figure b and figure c are Gel permeation chromatography of polymers $PEG_{2K}$-$PCL_{2K}$, $PEG_{5K}$-$PCL_{2K}$ and $PEG_{5K}$-$PCL_{5K}$, respectively.

three obvious peaks appeared in all three graphs; two of them are caused by the stretching vibration of the N–H group. This indicates the presence of an amino group, and it can be preliminarily judged that polymers with amino terminations have been synthesized. This is consistent with the chemical equation. Therefore, it can be inferred that PEG-PCL with the terminal amino group has been successfully synthesized [16].

*3.2 The analysis of gel permeation chromatography (GPC)*

As shown in Table 1, the molecular weight of the polymer obtained by the GPC test is close to the theoretical value; it is shown that the molecular weight of PEG-PCL synthesized by this method can be controlled in a certain range. The values of polydispersity (PDI) and Mz/Mw were in the range of 1 to 1.5; this indicates that the polymerization reaction is controllable and the synthesized polymers are homopolymers with narrow distribution.

As shown in Fig. 3, there was only one elution peak, further proving that the synthesized polymer was an amphiphilic block copolymer (PEG-PCL) rather than a mixture of MePEG and PCL [17]. The molecular weight distribution was maintained at about 1.3. This indicates that no depolymerization or crosslinking reactions have occurred.

Fig. 3 (A, B and C) are results of gel permeation chromatography of polymers PEG2K-PCL2K, PEG5K-PCL2K and PEG5K-PCL5K, respectively.

*3.3 The analysis of hydrogen nuclear magnetic resonance (1H-NMR)* The Fig. 4 is the ($^1$H-NMR) spectra of PEG2K-PCL2K polymer; the ($^1$H-NMR) spectra of PEG5K-

Table 1. Composition and molecular weight distribution of PEGm-PCLn

| PEGm-PCLn | Mn | Mw | MP | Mz | Polydispersity | Mz/Mw |
|---|---|---|---|---|---|---|
| PEG2k-PCL2k | 2972 | 3612 | 3439 | 4352 | 1.215521 | 1.204822 |
| PEG5k-PCL2k | 4737 | 6196 | 6791 | 7504 | 1.307921 | 1.211097 |
| PEG5k-PCL5k | 7373 | 10324 | 9480 | 13548 | 1.400165 | 1.312344 |

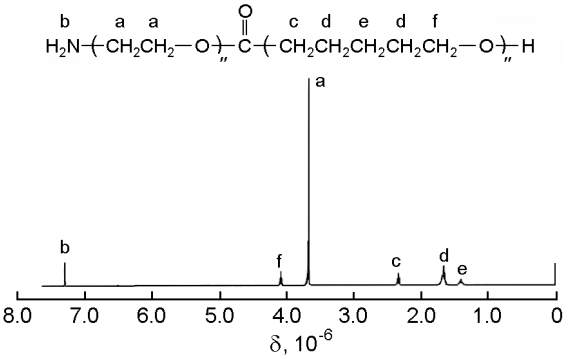


Fig. 4. Hydrogen nuclear magnetic resonance ($^1$H-NMR) spectra of polymers $PEG_{2K}$-$PCL_{2K}$2K.

PCL2K and PEG5K-PCL5K were similar to those of Fig. 4, so it was appropriately to analyze only Fig. 4.

The peak with a chemical displacement of $3.65 \cdot 10^{-6}$ is attributed to the proton peak of the methyl (a) in the chain segments of polyethylene glycol; the triple peak at $3 \cdot 10^{-6}$ is attributed to the proton (c); the triple peak at $4.1 \cdot 10^{-6}$ is attributed to proton (f); the multiple peak at $1.6 \cdot 10^{-6}$ is attributed to proton (d); the multiple peak in $1.4 \cdot 10^{-6}$ is attributed to proton (e). The results of hydrogen nuclear magnetic resonance showed that the product was an amphiphilic block copolymer (PEG-PCL) [18].

*3.4 The self-assembling of amphiphilic block polymers in water*

50 mg of the amphiphilic block polymers (PEG-PCL) was dissolved in 5 mL of THF, and then the copolymer solution was slowly dropped into 30 mL of water under the condition of intense agitation. The water-dispersion solution of the self-assembled polymer nanoparticles was dialyzed for 24 h in a dialysis bag (M WCO 4000) [19].

*3.5 Analysis of dynamic laser scattering (DLS) and Zeta potentiometer measurements*

The results of dynamic laser scattering (DLS) and Zeta potentiometer indicate that the size of the self-assembled nanoparticles is about 200 nm. The value of PDI below 0.2 indicates that the size of the self-assembled nanoparticles obtained by this method is uniform. The absolute value of Zeta potential was in the range of 35 to 40. It shows that the system has good stability and difficult to condense [20].

Table 2. Composition and molecular weight distribution of $PEG_m$-$PCL_m$n

| $PEG_m$-$PCL_n$n | Size, nm | Zeta, mV | PDI |
|---|---|---|---|
| $PEG_{2k}$-$PCL_{2k}$ | 156±23 | −35.46±4 | 0.142 |
| $PEG_{5k}$-$PCL_{2k}$ | 175±31 | −38.96±3 | 0.163 |
| $PEG_{5k}$-$PCL_{5k}$ | 186±35 | −34.72±4 | 0.192 |

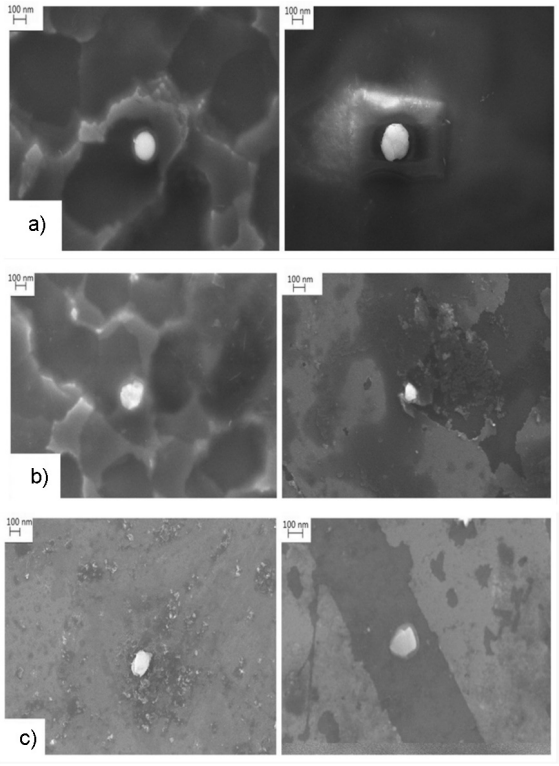


Fig. 5. Figure a, figure b and figure c are scanning electron microscope images of polymers $PEG_{2K}$-$PCL_{2K}$, $PEG_{5K}$-$PCL_{2K}$ and $PEG_{5K}$-$PCL_{5K}$ respectively

*3.6 Analysis by scanning electron microscopy (SEM)*

In the Fig. 5, the microstructures of the composites were analyzed by a scanning electron microscope. The surface morphology of nanoparticles is relatively regular, and the particle size range is close to the DSL test results. Thus, it is shown that the self-assembled nanoparticles have good surface morphology. The average particle size is about 200 nm.

## 4. Conclusions

In this paper, amphiphilic block polymers (PEG-PCL) with different molecular weights were synthesized by the method that uses potassium bis(trimethylsilyl)amide($KN(Si(CH3)_3)_2$) as a catalyst, ethylene oxide and ε-caprolactone as raw materials.

The testing and analyses have shown that the molecular weights and molecular weight distributions of the PEG-PCL, the micro-

structure, and the size of the nanoparticles formed by self-assembling basically reached the expected standard. This shows that the amphiphilic block polymers can be obtained by this method, and the molecular weight can be controlled flexibly [21]. However, the research on the PEG-PCL is far from complete, and there is still a lot of work to be done in the future.

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