

# Study on Recrystallization Process of Poly(DL-lactide)/Poly(ethylene glycol) Diblock Copolymer

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**Abstract:** Poly (DL-lactide)/Poly (ethylene glycol) diblock copolymer is successfully synthesized with mPEG and DL-LA as main raw materials, and the residual monomers of the polymer were removed by recrystallization. FT-IR is used to characterize the structure of the polymer. Gas chromatography is used to determine the residual monomers and residual solvent of the polymer. The solubility of polymer in different solvents was determined, and the effect of different solvent systems on the removal of residual monomers in copolymer were discussed. The results showed that the Poly(DL-lactide)/Poly(ethylene glycol) diblock copolymer was recrystallized with acetone/ isopropyl ether solvent system has the best ability to remove residual monomers, and the residual monomers of the obtained polymer are less than 0.01 wt%, the total residual solvent is only 0.24 wt%, and the productivity is as high as 95.5 wt%.

**key word:** Methoxypolyethylene glycols, DL-lactide, residual monomer, recrystallization

## 1. Introduction

Polyethylene glycol (PEG) is a widely used polyether polymer compound with excellent biocompatibility, blood compatibility, good hydrophilicity and softness. The introduction of PEG into the molecular structure of PLA can improve the disadvantages of PLA, such as poor hydrophilicity and compliance, and difficult control of degradation cycle, which is one of the main research directions at present. However, at present, Poly(DL-lactide)/Poly(ethylene glycol) diblock copolymerization is mainly obtained by solution polymerization or direct melt polymerization, and there may be unreacted monomers such as lactide, lactic acid, PEG, poly(lactic acid) initiated by trace water in the system, oxidation substances and other impurities in the polymer, which affect its use effect, so it is necessary to recrystallize the polymer to remove impurities and improve the purity of the sample.[1-6]

In this paper, polylactic acid - polyethylene glycol block copolymer was prepared by direct melt polymerization with polyethylene glycol monoformaldehyde and racemic lactide as the main raw materials. The solubility of block copolymer and racemic lactide in various solvents was studied, and the effect of solvent system on the residual monomer and yield was discussed. Because recrystallization can introduce organic solvents into the polymer, resulting in the polymer has a certain toxicity, so

the solvent residue in the re-crystallized polymer is monitored.

## 2. Experimental

### 2.1 Materials

Racemic lactide (DL-LA) purity >99.5%, provided by jinan daigang biotechnology limited public Company. Poly(ethylene glycol) methyl ether (mPEG, Mn=2000), ethyl acetate, toluene, dichloromethane, acetone, absolute ethanol, diethyl ether, n-hexane, isopropyl ether, stannous octanoate (SnOct<sub>2</sub>), etc. are all analytically pure (AR), which are provided by Sinopharm Chemical Reagent Co., Ltd. All raw materials must be dried before used.

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## 2.2 Instrument

Vacuum drying oven, Shanghai Senxin Laboratory Instrument; Fourier transform infrared spectrometer, model FT-IR 100, Perkin Elmer Company; Gas chromatograph, model 6890A, Agilent Technologies Inc.

## 2.3 Preparation of PLA-mPEG diblock copolymer

Adding DL-LA, mPEG and SnOct<sub>2</sub> into an ampoule bottle with a rotor according to a certain proportion, sealed it under a vacuum environment, then reacted at 145 °C for 24 h and cooled to obtain crude PLA-mPEG diblock copolymer. The polymerization equation was shown in Figure 1.

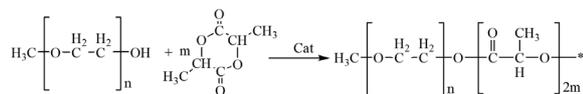


Figure 1. Polymerization equation

## 2.4 Recrystallization of PLA-mPEG diblock copolymer

A certain amount of crude PLA-mPEG diblock copolymer is added into the prefabricated organic solvent with the ratio of 1g/5 ml. After it is completely dissolved, a poor solvent is slowly added into the PLA-mPEG diblock copolymer solution, making the solution become turbid gradually, which the total calculated amount is 5-10 times the solution volume, and the PLA-mPEG diblock copolymer is slowly precipitated. Then, it is precipitated, filtered and dried at 45°C in a vacuum environment to obtain the high-purity PLA-mPEG diblock copolymer.

## 2.5 Performance characterization

Fourier transform infrared spectroscopy (FT-IR): The molecular structure of polymer was determined by FT-IR. Residual lactide monomers: Measured by gas chromatograph, determined according to General Rule 0521 of Chinese Pharmacopoeia (2020 edition), lactide content was calculated by peak area according to external standard method. Solvent residue: According to the second method of Chinese Pharmacopoeia General Rule 0861 (2020 edition), the solvent content was calculated by peak area according to the external standard method.

## 3. Result and discussion

### 3.1 Molecular structure characterization

The molecular structure of the prepared PLA-mPEG diblock copolymer was characterized by FT-IR, and the results were shown in Figure 2.

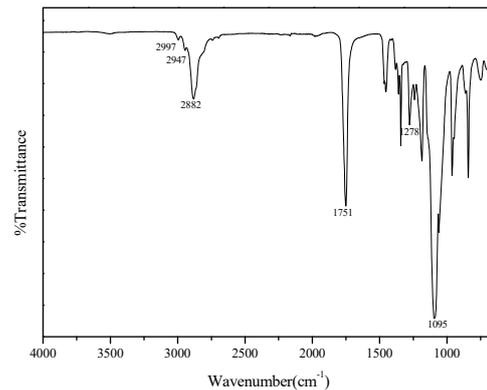


Figure 2. FT-IR of PLA-mPEG Diblock Copolymer

As shown in Figure 2, the characteristic peak of stretching vibration at 2997 cm<sup>-1</sup> is -CH<sub>3</sub>, the characteristic peak of stretching vibration at 2947 cm<sup>-1</sup> is -CH and the characteristic absorption peak at 2882 cm<sup>-1</sup> is -CH<sub>2</sub>. At 1095 cm<sup>-1</sup> and 1278 cm<sup>-1</sup>, there are asymmetric stretching vibration absorption peaks and symmetric stretching vibration absorption peaks of C-O-C respectively. At 1751 cm<sup>-1</sup>, the telescopic vibration absorption peak of C=O appears. No vibration absorption peak of the ring skeleton is found at 934 cm<sup>-1</sup>, which indicates that there is no ring structure. Since the residual monomers are small and difficult to monitor by infrared spectroscopy, further determination of the residual monomers by gas chromatography is required.

### 3.2 Solubility of PLA-mPEG diblock copolymer

In this paper, the solubility of polymer and racemic lactide in different solvents is compared, as shown in Table 1.

Table 1. The solubility of polymer and racemic lactide in different solvents

Number	Solvent type	PELA/(g/ml)	DL-LA/(g/ml)
1	dichloromethane	0.5	0.1
2	acetone	0.2	0.2
3	toluene	0.07	0.02
4	absolute ethanol	0.01	0.02
5	ethyl acetate	0.08	0.07
6	diethyl ether	<0.01	<0.01
7	isopropyl ether	<0.01	<0.01
8	n-hexane	<0.01	<0.01

As shown in Table 1, PLA-mPEG diblock copolymer and DL-LA have high solubility in methylene chloride and acetone, among which acetone has the strongest ability to dissolve dl-lactide. The solubility of PLA-mPEG diblock copolymer is not too high, so it is suitable for being a good solvent for recrystallization. The solubility of diethyl ether, isopropyl ether and n-hexane on PLA-mPEG diblock copolymer and DL-LA is not high, so it is suitable for recrystallization of poor solvents. Combined with the toxicity of various solvents and the degree of difficulty in the removal of polymer and other factors, choose dichloromethane and acetone the most recrystallized good solvent, choose n-hexane, diethyl ether and isopropyl ether as the poor solvent recrystallization, the next recrystallization test, select the best solution system.

### 3.3 Recrystallization of PLA-MPEG diblock copolymer

The content of residual monomers in PLA-MPEG diblock copolymer obtained by direct melt polymerization were as high as 1.89 wt%. Recrystallization was used to remove the residual monomers in the copolymer. Firstly, the polymer was completely dissolved in a good solvent, and then poor solvent was added to slowly precipitation to obtain a high-purity PLA-mPEG diblock copolymer. The effects of several different solvent systems on the removal of unreacted monomers from copolymers were compared, as shown in Table 2.

**Table 2.** Comparison of properties of PLA-mPEG block copolymer after recrystallization

Good solvent	Poor solvent	Appearance	LA residues/(wt%)	Total residual solvent/(wt%)	Productivity/(wt%)
dichloromethane	n-hexane	dark brown	0.55	0.57	90.0
dichloromethane	diethyl ether	brown	0.36	0.40	81.1
dichloromethane	isopropyl ether	buff	0.03	0.22	70.0
acetone	n-hexane	brown	0.55	0.56	88.9
acetone	diethyl ether	light brown	0.34	0.32	82.3
acetone	isopropyl ether	buff	<0.01	0.24	95.5

It can be seen from Table 2 that the residual monomers of polymer can be well removed by recrystallization. Among them, poly (DL-Lactide)/poly (ethylene glycol) diblock copolymer obtained by recrystallization in acetone/isopropyl ether solvent system has the highest purity, and lactide residue and total solvent residue are lowest, and the residual monomers are less than 0.01 wt%, which almost completely removed, and the yield is the highest, up to 95.5wt%; Methylene chloride/isopropyl ether has the second highest ability to remove residual monomers, but the lowest yield rate is only 70%. It can also be seen from Table 2 that whether the good solvent is of dichloromethane or acetone, the poor solvents use isopropane ether, both the residual monomers in PLA-mPEG diblock copolymer can be well removed. Considering the appearance and cost of the product, the best recrystallization system is acetone/isopropyl ether solvent system.

### 4. Conclusion

In this paper, PLA-mPEG diblock copolymer was successfully synthesized and residual monomers were removed by recrystallization. Acetone/isopropyl ether solvent system and dichloromethane/isopropyl ether solvent system had the best effect on the removal of residual monomers from PLA-mPEG diblock copolymer, and the total amount of residual solvent was the least, the content of residual monomers less than 0.01 wt% and 0.03 wt%, and the total residual solvent content was 0.24 wt% and 0.22 wt%. However, the productivity of PLA-mPEG diblock copolymer obtained by recrystallization of acetone/isopropyl ether solvent system was as high as 95.5 wt%, while the productivity of PLA-mPEG diblock copolymer obtained by recrystallization of methylene chloride/isopropyl ether solvent system was only 70 wt%.

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