

Synthesis And Application of Partial Block Polymers in Drug Delivery

Lishang Yue *

Northwestern Polytechnical University & Queen Mary University of London Engineering School,
Northwestern Polytechnical University, Xi 'an 710072, China

* Corresponding Author Email: yuelishang@mail.nwpu.edu.cn

Abstract. With the rapid development of modern medicine, the application of biodegradable polymers in drug delivery systems has received increasing attention. Due to their good biocompatibility and biodegradability, they can effectively deliver drugs to target sites while avoiding damage to other tissues. As a functional drug carrier, they have brought revolutionary changes to the field of drug development. Biodegradable polymers play a crucial role in drug delivery systems. Many drugs have excellent anti-cancer or other disease treatment effects, but cannot be directly applied in clinical practice due to low absorption rates or toxic side effects. Drug carriers can provide an effective delivery method for these drugs, achieving synergistic effects of multiple drugs and reducing toxic side effects in the human body. This article introduces four polymers, PLA, PEG, PCL, PEO, and the synthesis, modification, and application of three block copolymers of PLA-PEG, PCL-PEG, and PEO-PEG. It also summarizes the new progress of block copolymers in drug delivery and proposes some new issues and prospects for the synthesis of new drug carriers and the construction of drug delivery platforms.

Keywords: Block polymers, Drug delivery, Oncology, Medicine.

1. Introduction

Drug delivery plays a crucial role in drug development in the new era, with advantages such as high targeting ability and reducing drug toxicity and side effects. Block copolymers have played a key role in drug delivery. Block copolymers are special polymers that are connected by two or more different polymer chain segments with different properties. The choice of polymers allows block copolymers to have different properties, among which hydrophilicity/hydrophobicity, biocompatibility, and biodegradability are the research focuses.

For chronic disease treatment, oral administration is a commonly accepted delivery method because of its simple intake route and flexible location. However, the low solubility of hydrophobic drugs leads to poor absorption and bioavailability, requiring frequent administrations to reach the therapeutic dose, which increases the toxicity and side effects of the drugs and the financial pressure on patients [1]. Cancer poses a serious threat to human health and survival. Although surgical resection has the disadvantages of high difficulty, high risk, and easy recurrence, chemotherapy is still an indispensable treatment method [2]. Doxorubicin (DOX) is a broad-spectrum anti-tumor drug that is widely used in the treatment of various cancers. However, DOX causes oxidative stress and intracellular calcium ion disorders in heart tissues, leading to cell apoptosis and myocardial injury, which limits its application [3]. Curcumin (CUR) is a natural compound with an anti-tumor activity that also exhibits significant inhibitory effects on multidrug-resistant (MDR) cancer cell lines. DOX and CUR share the disadvantages of low water solubility and low bioavailability with other traditional chemotherapy drugs. Using amphiphilic polymers as carriers to construct drug-loaded colloidal particles is an effective way to improve drug solubility. The protective effect provided by block copolymers can reduce drug degradation and metabolism. In addition, block copolymers can dissolve drugs, achieve long circulation time, and can even be used as targeted drugs to reduce the adverse reactions of parent drugs and improve the therapeutic effect of drugs. This article will explore the synthesis, modification, and application of common biocompatible block copolymers in drug delivery.

At the same time, this paper will propose some new issues and prospects for the synthesis of novel drug carriers and the construction of drug delivery platforms.

2. Synthesis and Application of PLA-PEG in Drug Delivery

PLA belongs to the polyester family and is a polymer obtained by the polymerization of lactic acid as a raw material. The main production processes include direct polycondensation, a two-step process, and reactive extrusion. The raw material lactic acid used for synthesizing polylactic acid is abundant and renewable, and the products prepared can be biodegradable and circulate in nature, making it an ideal green polymer material. PEG is synthesized by the addition polymerization of ethylene oxide with water or ethylene glycol. It is widely used in rubber, pharmaceutical, electroplating, food processing, and cosmetics industries. PLA-PEG is a kind of biocompatible and biodegradable polymer material. Due to its hydrophilicity and ester affinity, it can be made into various forms of carriers, such as microspheres, micelles, gel, etc. Therefore, PLA-PEG block copolymers have broad prospects in drug delivery.

In the face of different diseases, such as lung cancer and liver disease, commonly used drugs include Doxorubicin (DOX) and DOX. However, DOX often has severe side effects (mediating oxidative stress and intracellular calcium ion disorders in heart tissue, leading to cell apoptosis and myocardial injury) and causes multidrug resistance, which greatly limits its clinical application. CUR can also cause damage to the liver and intestinal tissues. After high-dose oral administration of CUR, more than 70% of the drug is excreted in the feces, and then rapidly converted into inactive metabolites in the liver, leading to a reduction in plasma curcumin levels [3]. In order to reduce drug toxicity and improve drug absorption efficiency, there are various ways to modify the PLA-PEG end group, such as α -glycol end group modification, galactosamine modification, and methoxyl modification. In order to synthesize different end groups of PLA-PEG, the synthetic methods are also different. As for Figure 1, in order to synthesize different end groups of PLA-PEG, the synthesis methods are also different. For example, zinc lactate is prepared under vacuum conditions, or stannous caprylate is used as the catalyst and synthesized under vacuum [4,5].

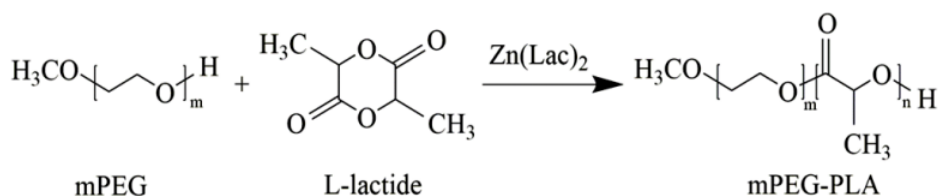


Fig. 1. Synthesis of PEG-PLA [5]

In terms of disease treatment effectiveness, drug-loaded PLA-PEG micelles significantly enhance the therapeutic effect compared to pure drugs. Yunchu Zhan et al. studied the anti-tumor activity of nanomicelles in a subcutaneous model. Tumor-bearing mice were divided into 6 groups ($n = 5$): NS, Vehicle, CUR/M, DOX/M, CURDOX/M, CUR-DOX/cyclo(ArgGly-Asp-d-Phe-Lys)cRGD-M. After different drug treatments, the tumor volume of each mouse was measured every 3 days. The drug-loaded group had almost no inhibitory effect on the tumor. Compared to single-drug or non-targeted dual-drug treatment, the tumor growth of the cur - dox /cRGD-M group was significantly inhibited. On the 14th day after inoculation, the targeted combination therapy group had the smallest average tumor volume, while the other groups were much larger. In addition, there was no significant weight suppression in the mice. Therefore, the article concludes that targeted combination therapy is more effective than single therapy in preventing primary tumor progression [3].

In terms of drug absorption, by simulating the pH values of the stomach and intestines, the proportion of curcumin released from PLA-PEG micelles is much smaller than that released from propylene glycol solution. When entering the simulated gastric environment, the amount of CUR released from the propylene glycol solution is approximately 1.5 times that of the PBS micelle group. These findings indicate that PEG-PLA micelles are stable in the gastrointestinal tract and systemic

circulation, so after oral administration, they can effectively deliver CUR to the treatment site. Furthermore, all of the CUR-loaded micelle groups have minimal cytotoxicity towards cells, indicating that the micelles do not affect membrane transport function. High Gal-modified PEG-PLA micelles can significantly promote intestinal penetration.

3. Synthesis and Application of PCL-PEG in Drug Delivery

Polycaprolactone (PCL) has been widely used in the field of drug delivery in recent years due to its excellent biodegradability and biocompatibility and has been approved by the US Food and Drug Administration [6]. PCL is obtained by ring-opening polymerization of ϵ -caprolactone and has good flexibility and processability, with a melting point of 59–64 °C, providing a basis for its application in drug controlled release. However, the hydrophobic surface of PCL is easily adsorbed by proteins and recognized and captured by reticuloendothelial cells in the body, resulting in a reduction in its circulation time in vivo. By modifying PCL and adding hydrophilic segments to prepare amphiphilic copolymers, PEG, as the most representative biocompatible hydrophilic segment, effectively applies PCL.

The biodegradable, amphiphilic, and easily synthesized poly (PEG-PCL) copolymer has potential applications in drug delivery systems. In the diblock copolymer of PEG-PCL, PEG forms the shell and PCL forms the core due to the hydrophilicity of PEG and the hydrophobicity of PCL. The hydrophilic and non-toxic properties of polyethylene glycol lead to the formation of micelles in an aqueous solution, which facilitates drug delivery, with the polymer acting as a carrier. The ratio of hydrophobicity and hydrophilicity within the diblock copolymer is influenced by the size of PEG, effectively impacting the drug delivery efficiency.

As shown Figure 2, PEG-PCL amphiphilic block copolymers are generally synthesized by ring-opening copolymerization of caprolactone monomers with stannous octoate as a catalyst and methoxy polyethylene glycol as a macromolecular initiator at high temperatures.

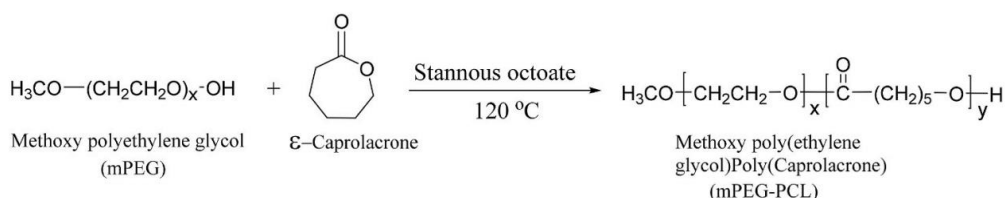


Fig. 2 Synthesis of PEG-PCL [7]

Another method for synthesizing PEG-PCL copolymers is to perform aminolysis on the PCL end group using 6-amino-1-hexanol, grafting the active hydroxyl sites onto the PCL chain. By reacting with succinic anhydride to introduce terminal carboxyl groups, PEG molecules are then immobilized in PCL through esterification, resulting in hydrophilicity.

Baicalin has a wide range of pharmacological effects, such as anti-inflammatory, anti-allergic, anti-endotoxin, antibacterial, antioxidant, anti-tumor and other biological activities. However, Baicalin has poor water solubility and low bioavailability. To ensure therapeutic efficacy, frequent administration is required, and the dose is high. After administration, the clearance rate is low, the half-life is long, and it is prone to liver and kidney toxicity [8]. Therefore, drug-carrying systems are needed to improve its hydrophobicity, and PEG-PCL is the best choice.

However, ordinary PEG-PCL cannot actively target tumor cells in the body, and cannot accumulate in large quantities at the tumor site solely by relying on high permeability and retention effects, resulting in reduced therapeutic efficacy. Therefore, it is necessary to perform targeted modification on the surface of PEG-PCL again, such as modifying RGD cyclic peptide, glycyrrhetic acid (GA). RGD cyclic peptide is a sequence polypeptide consisting of three amino acids Arg-Gly-Asp (Arginine-Glycine-Aspartic acid), which can specifically bind to 11 integrins and has excellent targeting effect. GA has pharmacological effects such as anti-allergic, antioxidant, liver protection,

anti-inflammatory, and anticancer effects. As shown the Figure 3, Runliang Feng et al. converted GA into 4-carboxybutyloxy-GA by O-acylation reaction with succinic anhydride. Then, using NHS and EDC as catalysts and reagents, a selective N-acylation reaction was performed on H₂N-PEG-PCL to obtain GA-PEG-PCL [2].

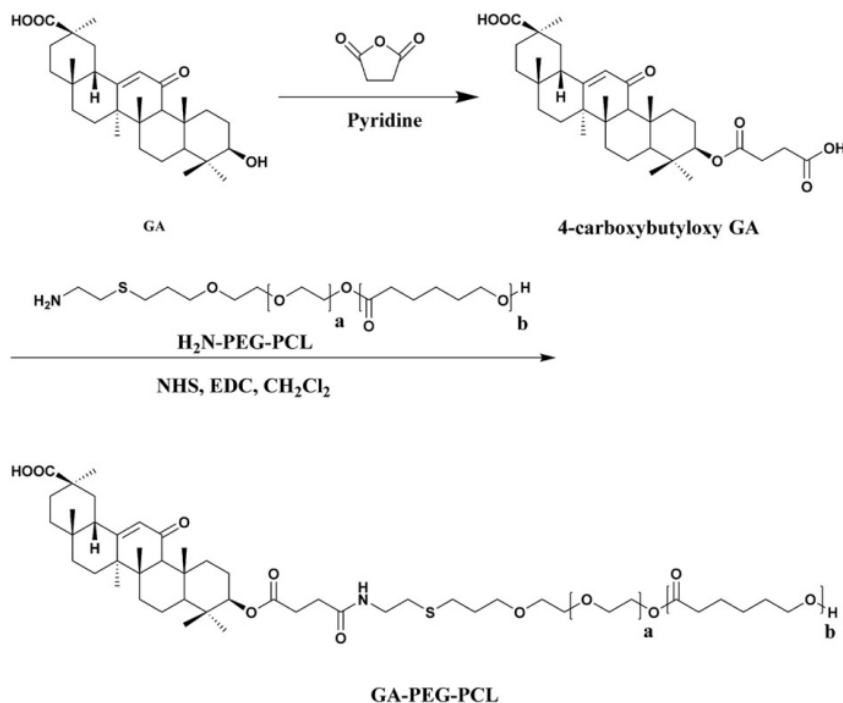


Fig. 3 Synthesis of GA-PEG-PCL [2]

4. Synthesis and Application of PEO-PPO in Drug Deliver

Polyethylene oxide (PEO) is one of the hydrophilic polymers used in controlled drug delivery systems, and has many positive attributes, including non-toxicity, high water solubility, and swelling ability. Propylene oxide (PO) is chemically reactive and prone to ring-opening polymerization. The difference in solubility between PEO and PPO segments in water makes this copolymer amphiphilic [9], which is the main driving force for the various phase behaviors exhibited by PEO-PPO copolymers. PEO-PPO copolymers can be self-assembled in selective solvents with flexibility, and are the most well-studied thermally responsive polymer family. Under appropriate conditions, PEO-PPO-PEO molecules self-assemble into nanometer-sized "core-shell" micelles, in which the hydrophobic PPO segments form a rather dense core and the hydrophilic PEO segments produce a rather bulky hydrated shell. When the temperature is below the critical micelle temperature (cmt), these "core-shell" micelles recover from their micellar array to the monomer state. The molecular weight of linear block polyethers, the length of PEO and PPO, and the ratio of EO/PO all significantly affect their aggregation behavior in aqueous solutions [10]. For block copolymers with the same PEO segment and different PPO segments, the cmc and cmt decrease with the increase of PPO content, allowing PEO-PPO-PEO to have various tunable properties.

Irinotecan (CPT-11) is a semi-synthetic derivative of camptothecin, with broad anti-tumor activity, and can be used in the treatment of non-small cell lung cancer, colorectal cancer, gastric cancer, ovarian cancer, and other cancers. The dose-dependent side effect of CPT-11 is gastrointestinal toxicity, and the incidence of delayed diarrhea after intravenous administration can reach up to 40%, which is the main reason for its clinical use being limited. PEO-PPO-PEO can effectively inhibit the active transport of CPT-11 out of cells against the concentration gradient, thereby reducing toxicity [11].

However, the application of PEO-PPO-PEO in drug delivery is problematic because they are not biodegradable. For PEO-PCL, the hydrolytically sensitive ester bonds between the hydrophilic PEO and hydrophobic PCL segments are usually located at the water/hydrophobic interface in the core-shell micelles, making them susceptible to hydrolysis, resulting in PEG block shedding and micelle instability. Therefore, PEO-PPO-PCL may be used to construct a highly stable and biocompatible drug delivery system.

As for Figure 4, the methyl group is connected to the end group of PEO-PPO, forming Me-PEO-PPO as an intermediate product. PEO-PPO-PCL is further synthesized by using Me-PEO-PPO as a precursor. With methanol as the precursor and potassium hydroxide as the catalyst, amphiphilic block copolymer Me-PEO-PPO was synthesized in a pressure reactor at 120-140 °C and 0.3 MPa pressure. Then, Me-PEO-PPO was used as the initiator and Sn(Oct)₂ as the catalyst to synthesize PEO-PPO-PCL by controlled ring-opening polymerization (ROP) of phcaprolactone [12].

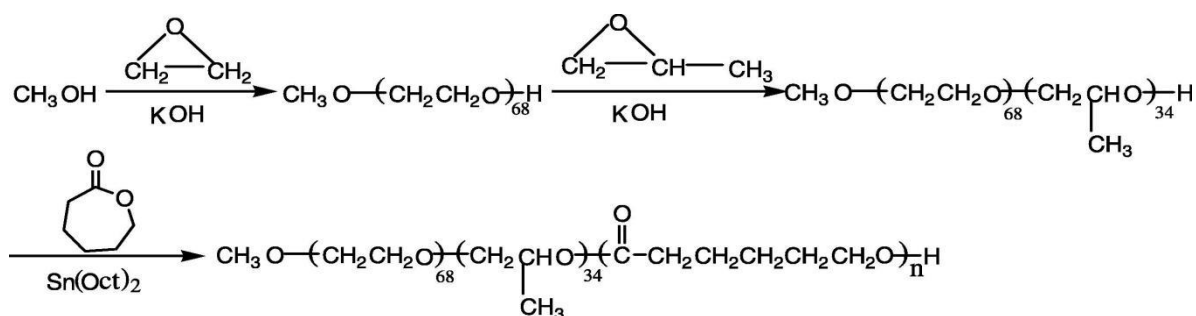


Fig. 4 Synthesis of Me-PEO-PPO [12]

Autophagy is an important mechanism of drug resistance, which promotes cancer cell survival in metabolic stress caused by anti-cancer drugs. Many anti-cancer drugs (such as DTX) can activate the autophagy pathway. Anti-cancer drugs are engulfed and cleared by intracellular lysosome vesicles. Chloroquine (CQ) is an autophagy inhibitor that selectively accumulates in lysosomes and inhibits lysosome acidification. The anti-tumor effect of CQ is mainly achieved by inhibiting autophagy. Therefore, CQ combined with anti-cancer drugs to inhibit chemotherapy-autophagy-dependent drug resistance and enhance the anti-cancer effect is a good choice. Therefore, using PEO-PPO-PCL polymer micelles to double-load DTX/CQ to enhance the anti-tumor effect has become a new approach for cancer treatment [13].

5. Conclusion

This article reviews the modification and synthesis methods of common block copolymers (such as PLA-PEG, PCL-PEG, and PEO-PPO), as well as their key roles in drug delivery. These specific block copolymers significantly improve the therapeutic effect by reducing the toxicity of anticancer drugs and hepatotropic drugs (such as curcumin, irinotecan, baicalin, etc.) and enhancing their targeting ability. However, current technology limits the ability of block polymers to encapsulate most drugs, and only some drugs can be applied through this method. In the future, it is expected that by continuously optimizing the modification of existing block copolymers and developing new block copolymers, the application scope of block copolymers in the field of drug delivery can be further expanded, so that more people can benefit from this technological progress.

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