Synthesis and Application of Amphiphilic Block Copolymer

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Abstract. The amphiphilic di- and tri-block copolymer is widely used to solve many seemingly intractable problems in our lives. They have the potential to help curing the cancel and some of them already in clinical application. Besides, it can work as a stabilizer of dispersions to disperse insoluble substance in certain solvents to make the substance work better. After decades of scientists' exploring, the living polymerization have been frequently used in living polymerization. In addition, the simple and efficient methods laying the foundation of the various application of amphiphilic di/tri-block copolymer. In this research, the living radical polymerization, such as reversible deactivation radical polymerization (RDRP) and ring-opening metathesis polymerization (ROMP), are mentioned. And the living anionic polymerization is the main approach synthesize a diverse of different block copolymers, where the reaction mechanism is further discussed in this research. After analyzing the properties of amphiphilic di- and tri-block copolymer to find why it can be used for drug delivery and as a stabilizer of dispersions, some applications for amphiphilic di- and tri-block copolymers will be introduced. With such advanced synthesis methods, however, the application of amphiphilic block copolymer is mainly in drug delivery. As a result, there might be some potential applications for amphiphilic di- and tri-block copolymer.

Keywords: Block Copolymer, Synthesis, Application.

1. Introduction

Common di- and tri-block copolymers include AB di-block copolymer, ABA tri-block copolymer and ABC tri-block copolymer, where A, B and C denoted polymer fragments composed of monomers chemically different, and A, B and C are combined by covalent bond. Since these di- and tri-block copolymer have simple structures (no branches), they are ideal models for studying morphologies. On the condition that the di/tri-block copolymer consist of both hydrophobic tail and hydrophilic head, the copolymer is amphiphilic in aqueous system. The advanced synthesis technologies show a key role in the wide application of amphiphilic di- and tri-block copolymer. The synthesis methods are versatile [1], including living polymerization by adding monomers in sequence, like RAFT, ROMP, ATRP and living anionic polymerization, using the end-functional groups to initiate a living polymerization, and linking two polymer chains by the end-group reaction.

Amphiphilic di- and tri-block copolymers are unique for self-assembly in selective solvent, which is very common in nature. Self-assembly is a spontaneous process that brings the whole system to equilibrium without the formation of covalent bond. Self-assembly endows the copolymer with a complex spatial structure, which in turn gives it unique properties. Due to their special properties, they have a great potentiality in application. Because of their similar structure to cell membranes, now many biodegradable amphiphilic di- and tri-block copolymer possess natural biocompatibility, where they have been widely used as drug delivery carriers after self-assemble into micelles, hydrogels, cubosomes and multilayer vehicles. Among all of which, micelles system is stable and easy to make, the drug will spontaneously insert into the micelle core through mixing the aqueous solutions of drugs and amphiphilic polymers, and the micelle size and critical micelle concentration (CMC) can be adjusted by blending excipient in different ratios. They offer an approach for the treatment of inflammation, diabetes, hypertension, and cancer. However, attempts are also being made to further improve its targeting ability to prevent premature release of drugs from damaging healthy cells. In addition, amphiphilic copolymers are often used as dispersants to disperse pigment molecules in aqueous solutions to prevent them from settling. Of course, there is still room for

improvement in coatings using amphiphilic copolymers as dispersants. For example, adaptability to weather, water resistance and anti-aging ability.

Nowadays the traditional approaches to cure the cancer are mainly chemotherapy and radiation, which will bring negative side effects to patients' health. In addition, drug therapy kills cancer cells as well as jeopardizing the lives of healthy cells. Scientists modified amphiphilic block copolymer and micells composed of amphiphilic block copolymer to make it ROS-responsive or pH-responsive. Then, the targeted therapy is realized by utilizing the characteristics of the tumor cell microenvironment with lower pH and higher ROS condensation. Therefore, by using polymer-based micells to encapsulate the drug and targeted release the it, the goal of killing tumor cells without harming healthy cells can be achieved. Moreover, the amphiphilic block copolymer (PBLG-b-PEG) physically modifies carbon nanotubes, which protects the original structure from damage and makes the carbon nanotubes stably disperse in organic solvents and water for a long time, thereby improving the carbon nanotubes. Further research found that PBLG-b-PEG can form aggregates with helical microstructure on the surface of CNTs in water system. And the helical structure is related to the molecular weight of the polymer and the size of the carbon material. For example, as molecular weight of copolymer PBLG decreases, the helical structure shifted to a smooth fibrous shape, while the helical structure of the increasing diameter CNTs tended to be abacus bead-like. Relying on the dynamically tunable properties of this morphological structure, the amphiphilic block copolymers have important significance for the preparation of new nanomaterials.

This research will introduce the synthesis methods of common block copolymers and their specific synthesis mechanisms. and will also analyze the physicochemical properties of the synthesized polymers. On this basis, this researh will further introduce the application of block copolymerization, to explore why it can be so widely used and the fields where it may be used in the future. Through this research, the authors hope to provide a new idea for the synthesis of novel block polymers and their performance regulation.

2. Synthesis

Advanced synthesis techniques for block polymers lay the groundwork for their widespread use. Understanding the synthesis mechanism of polymers can help to design new multifunctional block copolymer materials and tune their functional properties. As a result, this part will introduce the main synthesis method of block copolymer, and analyze the synthetic mechanism of each synthetic method. Ring-opening metathesis polymerization (ROMP) is from olefin metathesis, which has been widely used to prepare a diverse of different amphiphilic block copolymers. As shown in Figure 1, it illustrates the mechanism of ROMP. In the ROMP, transition metal complexes are used as the catalysts. With the efforts of scientists for many years, people have a better understanding of ligand effects and the reaction rates of ROMP have been greatly improved. The monomers for ROMP are cyclic olefins whose products have a good stability [1].

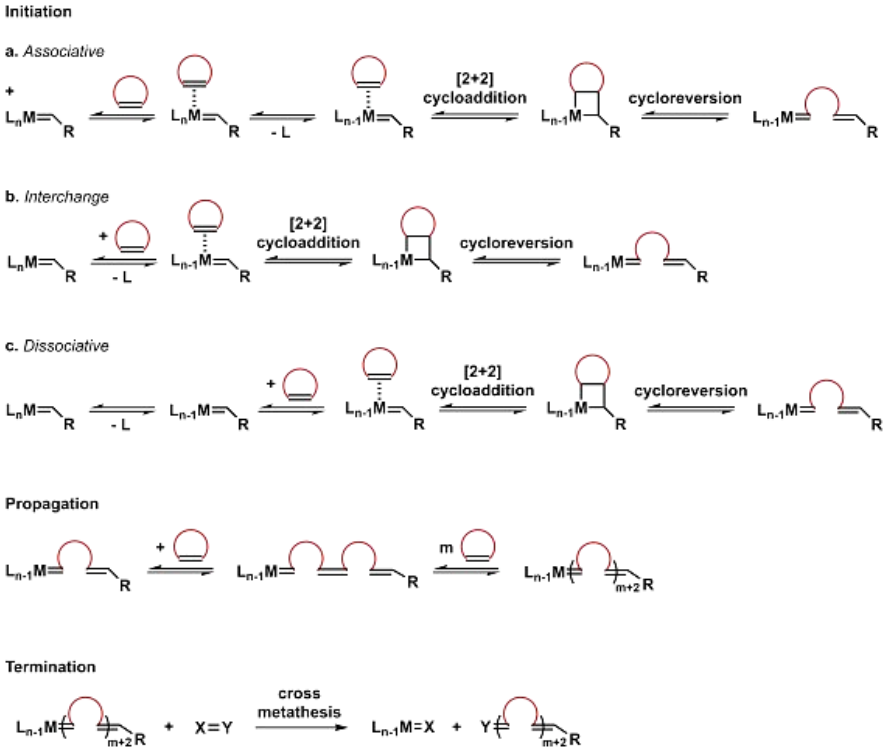

Figure 1. The synthesis mechanism of the ROMP [1]

The living polymerization, whose most prominent property is the chain growth will resume after adding more monomers, is frequently used for making copolymers. Definite homopolymers and copolymers consisted of simple dienes and substituted styrene, besides a variety of functional monomers, can be polymerized precisely by living radical polymerizations. As is declared in the persistent radical effect principle, the reactions are greatly inclined to produce the cross-reaction products while there nearly has no self-termination products of the transient radicals, regardless of when and how fast the persistent radical and transient radicals formed [2]. The low molecular compounds or longer chains R_n-Y, where $n \geqslant 0$, is the derivation of carbon centered radicles. The R_n· is the transient radical while the Y· is the persistent radical. To some extent, the dormant polymer is living for it can keep growing until the monomers run out, and restart growing after adding monomers. The termination products are nearly absent according to the persistent radical effect principle. As a result, the polymerize will go on without self-termination.

About 40 years ago, Ostu came up with a possible approach to realize the living radical polymerization based on the persistent radical effect, and successfully achieved the features of living and controllable polymerization. However, the conventions and the molecular weight were low [3]. In 1985, Rizzardo et al. uses alkoxyamines as initiator to bring living polymerization which is controlled, and they denoted that a radical adds to monomers forms upon dissociating with R groups [4]. Then in 1993, Georges et al. adopted nitroxide radical triggered by TEMPO and dibenzoyl peroxide in styrene, which means they didn't use alkoxyamines as initiators [5]. Under the given condition, the free benzoyloxy radicals add to the styrene monomers superior than the single alkoxyamines, then the adduct will combine with nitroxide radical.

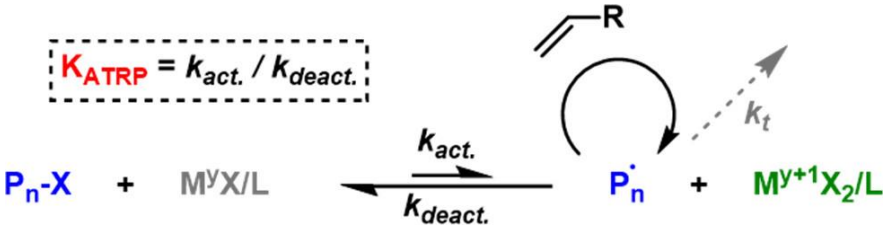

Figure 2. ATRP process-based living radical polymerization [6]

There are some general requirements to achieve the living radical polymerization, as show in Figure 2. Firstly, it is clear that R· is supposed to be persistent, as a result, no termination occurs. If the concentrations of the radical polymer chains are too high, the termination will occur, as a result the polymer chain is no longer living. I-R and P-R (where P denotes all the polymer chains combing with R) must be inert to make sure both the concentration of I· and R· are both low. In another word, the reactions must satisfy ($k_{ATRP}=k_{act}/k_{dact}$ <<1). When making block copolymers, the most commonly used method is to add the second monomer after the first monomer is polymerized and purified. In order to make the homopolymer can reinitiate after adding catalysts (transition metal M) and monomer, the end group fidelity is the higher the better. Although the termination has been inhibited in ATRP, the end group fidelity will still be reduced due to the excess of M^{y+1}, resulting in a decrease in the efficiency of the reaction. There are many methods to solve this problem, such as initiators for continual activator regeneration (ICRA) [6]. In addition, the better the selectivity and activity of the catalyst, the more conducive to industrial production [7]. The ATRP can be used to prepare different monomers. When synthesizing block copolymers, the order of synthesis is methacylate > methacrylamide > styrene > acrylate > acrtmide.

Among all the reversible deactivation radical polymerization (RDRP) process, the widest range of monomers, including vinyl esters and vinylamides, which can't be controlled by NMP and ATRP, can be controlled by RAFT process. In addition, the polymerization rate does not change much compared with the traditional polymerization since the concentration of free radicals does not increase due to RAFT. The formation of dead chains can't be avoided in RAFT process even with the addition of RAFT agents, and the magnitude will be affected by RAFT agent and monomer. The R group should have good leaving ability. Therefore, it can play an efficient role in the initiation and re-initiation process. In addition, considering that the block gain in the first step will perform as the R group in the second initiation, the block with better leaving ability should be synthesis first. RAFT process is the most general and easiest way to synthesis block copolymers. As shown in Figure 3, for the synthesis of AB di-block copolymer, the second monomers are supposed to be added after purification. The first two steps of the synthesis of ABA tri-block copolymer are similar to AB di-block copolymer. However, The ABA tri-block copolymer virtually formed after the termination. Because of the selection of the RAFT agent, the termination products are too little to affects the quality of final products [7].

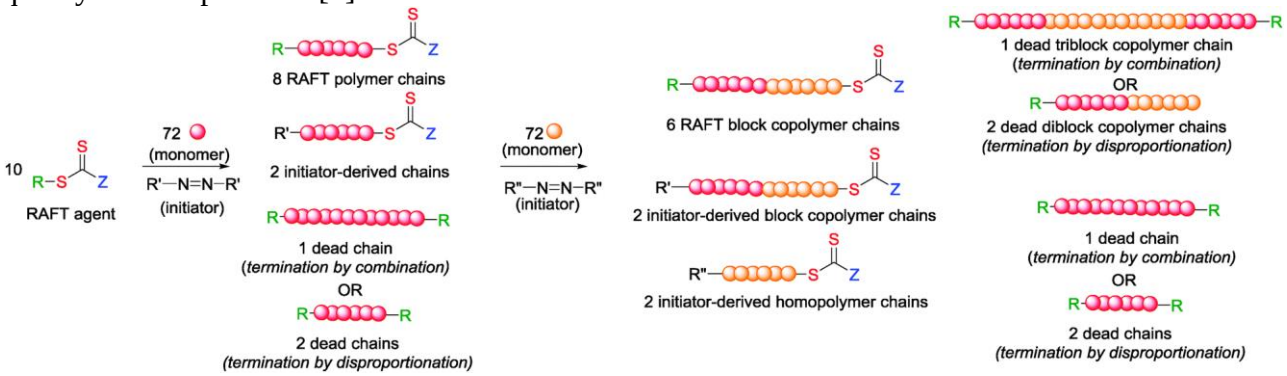

Figure 3. Synthesis ABA tri-block copolymer in the process of RAFT [7]

The living anionic polymerization is a very straightforward way to make block copolymer by adding the monomers in the sequence of the blocks in copolymer with controlled molecular weight. However, monomers have electron donating/withdrawing groups can be prepared through anionic polymerization, including styrene, 1,3-dienes and acrylonitrile. Instead of adding monomer B to living polymer made by A, by making a polymer with a functional group that can initiate B to make AB di-block copolymer is also available. In addition, preparing two polymers with functional groups that can react with each other is also a way to make AB di-block copolymer. There are also two ways to make ABA tri-block copolymer, the two-stage process and three-stage process. First, the two chemical different monomers are polymerized into a living block polymer chain with active ends through active ion polymerization, and then the two long chains are combined to terminate with the

help of bifunctional linking reagent to form an ABA triblock copolymer, or by using a difunctional initiator to make an ABA triblock copolymer by adding two monomers respectively in two steps.

3. Application

"Amphiphilic", which literally means "love both", is the key to the self-assembly of amphiphilic block copolymer. It can be used to prepare a diverse of different nanostructures, such as micelles, nanogels, polymersomes and multilayer vehicles with varying size. Meanwhile, these nanostructures can be made responsive by further modification. In addition, amphipathic properties make the block copolymer surface-active, and as a result, the amphiphilic block copolymer can act as a membrane-forming agent, modifier of surfaces and stabilizer of dispersions. When applying amphiphilic block copolymer as the carriers of the drugs in the drug delivery system, the carriers is always expected to have good biocompatibility, responsiveness and stability. Drugs that kill cancer, like doxorubicin (DOX), also threaten the survival of healthy cells. Besides, as most of the fluorescent probe has poor solubility in aqueous solution, polymer-based micelle should be used to transport the bioimaging probes.

The tumor microenvironment has a lower pH and a higher reactive oxygen species condensation. Therefore, reactive oxygen species (ROS)- and pH-responsive drug delivery system are usually applied for cancer treatment. For example, Bai et al. come up with the idea of combining bioimaging and drug delivery to achieve the effect of killing cancer cells and showing the location of drugs [8]. In their conception, AzPOH was first reacted with acryl chloride, and then monomers with Dithiomaleimides (DTMs) functional groups were obtained through click reaction. Using acid-sensitive PDPA-MA or PDBA-MA to combine with hydrophilic PEG chains, and then with poly (DTM-MA). Finally, acid-sensitive amphiphilic triblock copolymers with fluorescent performance were obtained. Then dissolve the PEG-b-poly(DPA-co-DTM) and DOX together to make drug-loaded micelles in dark condition. As shown in Figure 4, the micelles will release the DOX as soon as they enter the tumor cells in respond to the pH level.

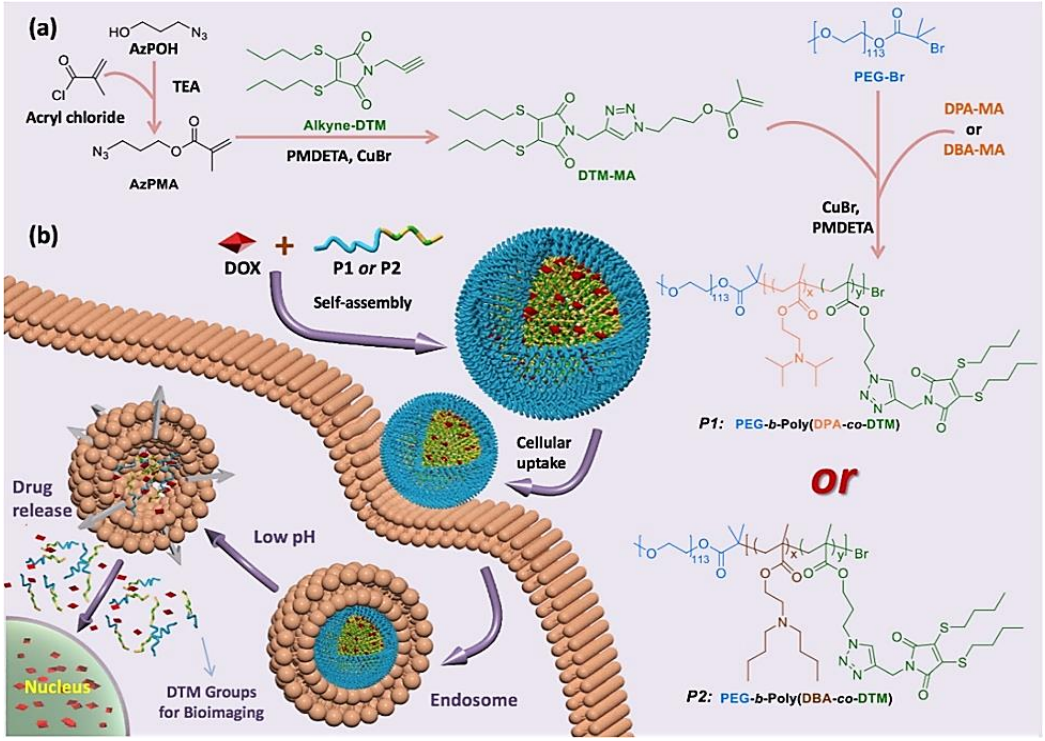

Figure 4. The use of the prepared PEG-b-poly(DPA-co-DTM) in ROS-responsive drug delivery system [9]

Wang et al. used the cinnamaldehyde (CA) to develop a new drug delivery, which can kill cancer cells by generating ROS in mitochondrion [9]. However, the aldehyde group in CA will be oxidized immediately, which limited the use of CA. As a result, they converted the aldehyde group to form a structure, such as TA and gain TA-CA. They use RAFT polymerization to synthesis the block copolymer. First, they link the anti-tumor drug with copolymer through TA-CA by integrating TA-CA in the macromolecular chain transfer agent. Then, they introduce a pH-sensitive N,N-diisopropylanmine (DPA) moiety into the copolymer, which will be positive charge in acid condition. As the membrane of mitochondria is negatively charged, there will be a strong interaction between micelles and the membrane of mitochondria.

The amphiphilic property enables the used block copolymer to stabilize the dispersion in the solvent. In other words, it can act as a dispersant. For example, single wall carbon nanotubes (SWNTs) have may awesome properties and many potential applications. However, the insoluble nature of the prepared SWNTs in most solvents hammered its application. Although people have found that the dispersant can improve the dispersion of SWNTs, few can stabilize SWNTs in polar as well as nonpolar medium and don't destroy the structure of SWNTs. Shin et al. reported a new approach to disperse SWNTs in polar and nonpolar medium [10]. In this work, amphiphilic block copolymer micelles were used to achieve the set goals because to the introduction of these copolymer micelles can attach to the SWNTs surface. In addition, amphiphilic block copolymer dispersant is also very important for coating technology, for they can hammer the sedimentation of pigments particles and make the system stable.

4. Conclusions

In summary, this research presents the virous block copolymers synthesis methods and their applications for biomedical field. The synthesis methods of amphiphilic di- and tri-block copolymer is various living polymerization, they have different mechanism and can be used for a diverse of various conditions and for monomers with different structure. And the advanced synthesis methods can be also used to play a key role in the application of amphiphilic di- and tri-block copolymer, which are very important parts of polymer science. Based on the properties of amphiphilic di- and tri-block copolymer, many scientists come up with a variety of amazing employments of them, including drug delivery, dispersant and so on. However, the application of these block copolymers is commonly used in biomedical fields, such as for drug delivery. Although it has been widely used in this area, the application of amphiphilic di- and tri-block copolymer is still waiting for more innovation.

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