

The Importance of AI Algorithm Combined with Tunable LCST Smart Polymers in Biomedical Applications

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Abstract: Smart polymers, also known as stimulus-responsive polymers or environmentally sensitive polymers, are a class of polymers that exhibit changes in their physical and chemical properties in response to various external stimuli, including small physical and chemical changes in the environment. These stimuli can trigger changes in the properties of the smart polymer, such as phase, shape, optics, mechanics, electric field, surface energy, reaction rate, permeability, and perception. Due to the biological sluggishness of conventional smart polymers, different manifestations of polymers are realized through the combination of AI technologies, including water solubility, adsorption on the surface of the carrier, or part of the cross-linked polymer system. While the definition of smart polymers can include two-phase transition processes such as glass transition and melting, the focus of research in the field of smart polymer systems is their behavior in polymer aqueous solutions, interfaces, and hydrogels. In this paper, a noteworthy smart polymer Low critical solution temperature (LCST) polymer is analyzed based on the combination of AI algorithm and deep learning. By carefully designing and modifying the structure of the polymer, the researchers can adjust the LCST to approximate the physiological temperature, making it suitable for potential biomedical applications. Looking ahead, an important development direction is the creation of LCST-type polymers that exhibit a variety of responses to different stimuli, while also improving their biodegradability. Incorporating AI into the design and modification of these polymers could facilitate the development of advanced smart materials with enhanced properties and functionality, opening up new possibilities in areas such as biotechnology, drug delivery, and response materials.

Keywords: Smart Polymer; LCST; Artificial Intelligence; Adjustable Heat.

1. Introduction

Stimulus-responsive polymers, also known as "smart" polymers, exhibit responses to various external stimuli, including changes in temperature, pH, ionic strength, REDOX reactions, light, shear stress, enzymes, and more. Artificial intelligence (AI) algorithms can be applied to the design and simulation of smart polymers, thereby accelerating the development of new materials with specific responsive properties [1]. Techniques such as deep learning, machine learning, and quantum chemical computing can aid in predicting the behavior of smart polymers under different environmental conditions. This predictive capability assists in controlling and ensuring the desired intelligent properties of the polymer for practical applications. Temperature-sensitive polymers exhibit changes in structure or solubility with temperature, with the temperature at which these changes occur referred to as the transition temperature. AI algorithms can expedite the development and optimization of smart polymers, enhancing their performance and controllability [2-3]. This, in turn, expands the potential applications of smart polymers across various fields, fostering progress in materials science and engineering and offering new opportunities for innovative material design and utilization.

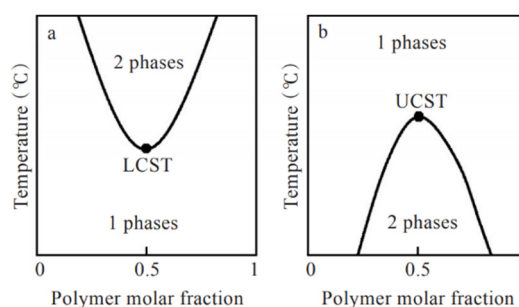


Figure 1. Temperature sensitive polymer dissolved phase diagram: (a) LCST type polymer, (b) UCST type polymer

The combination of AI and LCST polymers, as explored in this study, holds significant potential for applications in diverse fields, including drug delivery, biomedicine, smart coatings, smart materials, and flexible electronic devices. AI enables real-time control and optimization of LCST polymers in these applications [4]. Generally, LCST polymers can be categorized into two types: those with a low critical solution temperature (LCST) and those with a high critical solution temperature (UCST). LCST-type polymers dissolve and become uniform in a solution when the temperature is below their LCST, while phase separation occurs when the temperature is above the LCST. UCST-type polymers completely dissolve and become uniform at temperatures above their UCST. LCST and UCST represent critical

temperature points for polymer dissolution, respectively.

Among them, the application research of LCST polymer has received more attention. In this paper, the temperature-sensitive mechanism and classification of LCST polymer are introduced. The application of LCST polymer in drug delivery, gene therapy and tissue engineering are discussed. The future development direction of LCST polymer is also prospected [5-6].

2. Related Work

Thermal sensitive polymer materials are a kind of intelligent materials, which show the characteristics of sensitive response to temperature stimulation. Among them, polyn-isopropylacrylamide (PNIPAAm) and polyethylpyrrolidone (PVP) are representative members of thermal sensitive polymers. These materials show remarkable property changes over a specific temperature range, and the combination of artificial intelligence (AI) brings new prospects for their research and application. By combining artificial intelligence, it is possible to more quickly understand and predict the behavior of heat-sensitive polymer materials under different temperature conditions[7]. AI algorithms can analyze large amounts of experimental data to help researchers determine key properties of these materials, such as temperature response ranges and transition temperatures. This ability is critical for material design and performance optimization, helping to adjust the specific temperature response of thermosensitive polymers to meet the needs of different applications. In terms of applications, thermosensitive polymer materials have a wide range of potential in the fields of medicine, biomedicine, drug delivery and smart materials.

With the wide application of thermosensitive polymers in various fields such as chemistry, biology, textiles and so on, a single thermosensitive homopolymer can no longer meet the requirements, such as PNIPAAm, when used as a catalyst carrier, some reactions need to be carried out at a temperature above 32°C, but the LCST of PNIPAAm is 32C, so it can be dissolved in water at a higher temperature. It is necessary to improve its LCST: For this reason, the LCST of temperature-sensitive polymers is adjusted by different methods to broaden the range of use of temperature-sensitive polymers. Taking PNIPAAm as an example, the specific adjustment methods are classified as follows [8].

2.1. Random Copolymerization with Other Monomers

By this method :() changing the composition to change the hydrophilic ratio of the copolymer, further exploring the thermal sensitivity mechanism, changing the LCST of the NIPA copolymer to expand the temperature application range of the temperature-sensitive materials, and studying the relationship between structure and performance. (2) Expand the application function of copolymer, so that it is not only heat sensitive, but also sensitive to pH, light and other functions[9-11]. One approach is to increase LCST by random copolymerization with hydrophilic monomers, which can be mainly divided into strong electrolyte type, weak electrolyte type and non-electrolyte type." The commonly used electrolytic hydrophilic monomers mainly include acrylic acid (AA), methacrylic acid (MMA), 2-propylamine-2-methyl-1-propyl sulfonic acid (AMPS), etc. The commonly used non-electrolytic hydrophilic monomers mainly include

NN dimethylpropenylamine DMAM, AM, Z diol, etc.

2.2. Macromolecular Surfactant

As viscosity modifiers in aqueous solutions, hydrophobic modified water-soluble polymers are becoming more and more mature in theoretical research, and their applications are becoming more and more extensive. The aqueous solution of the modified polymer exhibits great viscosity above the polymer limit concentration, because the modified polymer has a greater tendency of intermolecular aggregation.

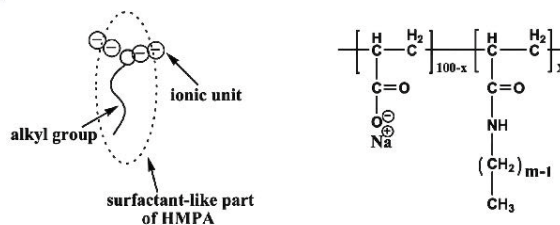


Figure 2. Chemical formulas of the random HMPA copolymers used in the present study and a schematic depiction of their surfactant-like part

The hydrophobic groups are generally long alkyl chains. They are called polymer surfactants because they have a structure similar to that of surfactants, that is, long alkyl chains connected with polar heads, as shown in Fig.2. Therefore, it also has similar effects to surfactants.

2.3. Reversible Temperature-sensitive Transition of PNIPAM

In aqueous solution, the hydrophilic groups in the polymer can form a large number of hydrogen bonds with water molecules, and the formation of hydrogen bonds is an exothermic process. Therefore, $\Delta H < 0$: the intermolecular hydrogen bond prevents the water molecules from forming a hydration layer around the polymer chain, and the freedom of water molecules is reduced, so the $-\Delta S$ of the system is > 0 . When the temperature is low, the $-\Delta S$ value is small, the system $\Delta G < 0$, and the polymer-water system is a homogeneous solution[12]. When the temperature increases, the molecular kinetic energy increases, the hydrogen bond stability between the hydrophilic groups on the polymer and the water molecules decreases, the hydrogen bond interaction weakens, the thermal effect decreases, and the ΔH value decreases. When the temperature rises, the $-\Delta S$ value increases, and the system $\Delta G > 0$ [13]. The macro performance is that the polymer precipitates from the solution, and the system becomes cloudy, so LCST is also called "cloud point". Phase separation is mainly caused by the increase in temperature and the change in entropy of the system, so the appearance of LCST is attributed to "entropy drive".

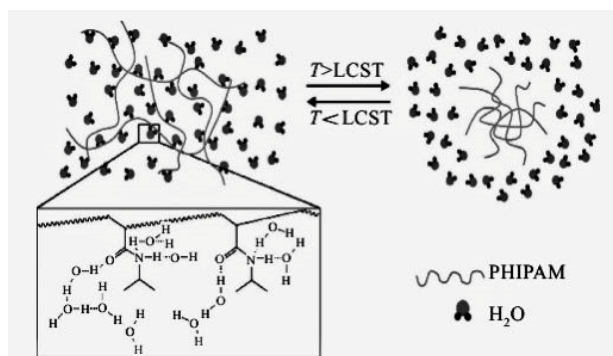


Figure 3. Schematic diagram of reversible temperature-sensitive transition of PNIPAM

3. Methodology

Based on the above research background, in this paper, PEGA and ethoxy ethoxy acrylate (DEGA) were selected as temperature-responsive monomers to replace the traditional n-isopropyl acrylamide (NIPAM). The LCST regulated temperature-responsive CCSP was prepared by the "alarm priority" approach and RAFT polymerization method. Since the LCST of PEGA and DEGA homopolymers is 90 C and 2621-2, respectively, the LCST of CCSP can be changed by controlling the ratio of the amount of PEGA and DEGA in CCSP. In addition, the pH of the solution will affect the electrification of the polymer and thus change its hydrophilicity, which will also play a regulating role in the LCST of the obtained CCSP.

3.1. Data Test

Synthesis of CCSP based on LCST: P(PEGA-CO-DEGA)-1 was used as an example to prepare P(PEGA-CO-DEGA) CCSP. 500 mg P(Pega-CodeGA-1) (0.05 mmol) and 195 mg crosslinker DVB (1.5 mmol) were synthesized. 80 mg flexible monomer DMAEMA (0.5mmol) and initiator AIBN were added to 25 mL round-bottomed flask successively, and then 8 mL alcohol was added. After being fully dissolved, vacuum was repeatedly vacuumed and filled with nitrogen for 3 times to remove oxygen.

After the reaction in 70 C oil bath for 24h, quenched with ice bath, yellow clarified solution was obtained. The reaction solution was poured into a 1.4x10 intercepted dialysis bag for dialysis. First, ethanol was selected as the dialysate, and the dialysate was changed once every 8h for 3d. Then, the dialysate was changed from ethanol to water for 3d dialysis once every 8h. Finally, the nuclear cross-linked star polymer, named CCSP-1, was prepared by freeze-drying.

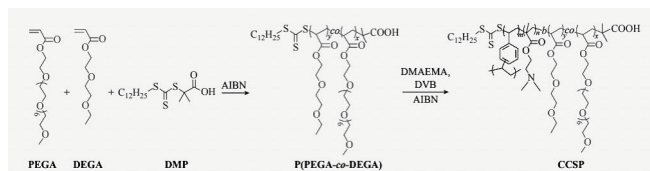


Figure 4. Synthetic routes of P(PEGA-co-DEGA) and CCSP

In the same way, CCSP was prepared by the reaction of P(PEGA-co-DEGA) -2 and P(PEGA-co-DEGA) -3 with DVB and DMAEMA, respectively, and named CCSP-2 and CCSP-3.

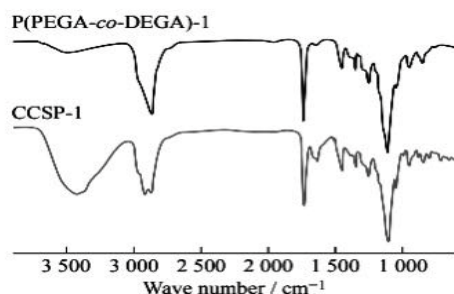


Figure 5. FT-IR spectra of P(PEGA-co-DEGA)-1 and CCSP-1

3.2. Data Result

From the difference between the characterization of P(PEGA-co-DEGA) and CCSP, it can be seen that there are two peaks in the outer arm P(DEGA-co-DEGA-1) at 1730 and 1100 cm-1. The elastic vibration absorption peaks of ester group (O -- C = O) and ether bond (C = O -- C) in

thermosensitive monomers PEGA and DEGA, respectively. When DVB and DMAEMA were added to CCSP-1, the out-of-plane deformation vibration of para-substituted benzene appeared at 835 cm-1, and the out-of-plane deformation vibration peak of para-substituted benzene appeared at 796 cm-1 and 709 cm-1. Moreover, the characteristic vibration peaks attributed to C-CH3 and C-H bonds in DMAEMA appear at 2927 cm-1 and 2860 cm-1, and the vibration absorption peaks of tertiary amino (-N (CH3) 2) appear at 1150 cm-1. The results indicated that CCSP was successfully prepared.

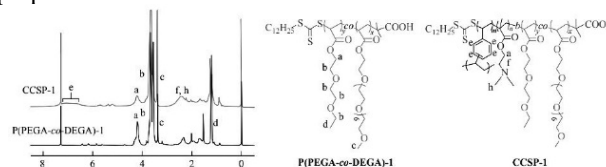


Figure 6. 1H-NMR spectra of P(PEGA-co-DEGA)-1 and CCSP-1

From the nuclear magnetic resonance hydrogen spectra of P(PEGA-co-DEGA) -1 and CCSP-1, it can be seen that The peaks at chemical shifts 4.27 (a), 3.71 (b), 3.36 (c) and 1.21 (d) of the two are attributed to the chemical shifts of methylene and methyl groups on the PEGA and DEGA chains, respectively[14-15]. Compared to the linear outer arm, the chemical shift of the protons in DVB's benzene ring is observed 6.5 ~ 7.2 (e) and the two proton peaks are also observed 2.43 (h) and 2.59 (f). The chemical shift of hydrogen on methyl group (-CH2-N (CH3) 2) and methylene group (-CH2-N (CH3) 2) in DMAEMA, respectively, further explain the results of thermal regulation of polymers in the context of big data algorithms such as artificial intelligence. The synthesis of the monomer containing the heat-sensitive stellar nucleus crosslinked polymer is the extra-arm and DVB DMAEMA core.

4. Conclusion

In addition to the above, LCST polymer has unique temperature sensitivity and good biocompatibility, and has broad application prospects in biomedical fields such as drug delivery, gene therapy and tissue engineering. LCST delivers the drug to the desired location during drug delivery and provides the right concentration at the right time. The problems that need to be solved in drug delivery system include low solubility of drugs, environmental or enzymatic degradation, excessive clearance rate in vivo, non-specific toxicity, and delivery barriers in vivo.

With the help of AI, intelligent control of these materials can be achieved, allowing them to play a greater role in drug release in the medical field or self-assembly in smart materials. In addition, research methods combined with AI can also help accelerate the development of new heat-sensitive polymer materials, providing more opportunities for innovation and solving practical problems. However, although the research of LCST polymer has made some progress, there are still some problems in LCST polymer at present, mainly including the following two points :1) LCST polymer only responds to temperature, its function is relatively simple, but the stimulation modes in the environment are diverse, and multiple stimulation modes coexist; 2) Most LCST-type polymers are difficult to biodegrade, limiting their application in the biomedical field.

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