HIGH SCHOOL EDITION
Journal of Student Research
Volume 13 Issue 4 (2024)

Biodegradable Thermo-Responsive Smart Materials in Drug Delivery Application

Xiaoxiao[1] Song and Jingya Qin[#]

[1]Shenzhen Middle School, China
[#]Advisor

ABSTRACT

Smart materials allow more effective, targeted, and regulated release of medicinal medicines because of their capacity to react to environmental stimuli including temperature, pH, and light. Over the past few decades, this feature was used to completely transform the medication delivery industry. Understanding the function of integrating thermo-responsive and biodegradable materials has been partially accomplished by recent study. Specifically, when biodegradable polymers like poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and polycaprolactone (PCL) are combined with thermoresponsive materials like poly(N-isopropyl acrylamide) (PNIPAM) and poly(N-acryloyl glycinamide) (PNAGA), a medication will release when the temperature reaches a certain point and then break down into non-toxic byproducts. This approach not only reduces chronic accumulation and related negative effects, but also increases safety and biocompatibility. In addition, external factors such as localized thermal shock can enhance medication release even more, targeting its distribution to certain locations and enhancing therapeutic outcomes. In this study, we will examine the most recent developments and difficulties in the application of thermoresponsive, biodegradable smart materials for drug delivery systems, and we will talk about how these materials may be used to improve treatment plans.

Introduction

The desire for more sophisticated therapeutic agents has led to considerable advancements in the field of medication delivery. Designed materials that may significantly alter one or more of their characteristics in a regulated manner in response to external stimuli are referred to as stimulus-responsive materials, or smart materials. They were extensively employed in medication delivery systems to lower drug toxicity and improve therapeutic efficacy. (Wang, 2014) Thermo-responsive smart materials have emerged as one of these stimuli-responsive materials that shows great promise, because they may be precisely tailored to the physiological circumstances of the human body. These materials can undergo reversible phase transitions in response to temperature variations. (Kim, 2017)

Thermo-responsive polymers are characterized by their lower critical solution temperature (LCST) or upper critical solution temperature (UCST). At temperatures below LCST, the system is completely miscible in all proportions, whereas above LCST partial liquid miscibility occurs. An essential example of an LCST polymer is poly(N-isopropyl acrylamide) (PNIPAM), which has an LCST of around 32°C, close to the human body temperature. This property makes PNIPAM highly suitable for biomedical applications, particularly in drug delivery, where a slight increase in temperature can trigger the release of a drug payload at a targeted site, such as a tumor or inflamed tissue. (Lanzalaco, 2017) Conversely, polymers like poly(N-acryloyl glycinamide) (PNAGA), which exhibit UCST behavior, dissolve above a certain temperature and precipitate out when cooled, offering another mechanism for controlled drug release. (Xu,2018)

One of the primary advantages of using biodegradable thermo-responsive polymers in drug delivery systems is their ability to degrade into non-toxic byproducts after fulfilling their drug delivery function. (Chatterjee, 2021) This biodegradability reduces the potential for long-term accumulation and associated side effects, enhancing the

overall safety and biocompatibility of the drug delivery system. Biodegradable polymers such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), Polycaprolactone (PCL), and their copolymers have been widely studied for this purpose. When combined with thermo-responsive polymers, these materials can provide a dual function of temperature-triggered drug release and subsequent biodegradation, ensuring that the drug delivery system is both effective and safe. (Gandhi, 2015) Different environmental stimuli that may be accurately regulated make it easier to apply thermo-responsive biodegradable polymers in medication delivery. For example, drugs can be released from thermo-responsive carriers by applying localized hyperthermia or external heating equipment. By concentrating the drug release at the region of interest, this tailored method minimizes systemic adverse effects while simultaneously optimizing the therapeutic efficacy of the medication. (Lanzalaco, 2017)

This review, regarding the use of biodegradable thermoresponsive smart biomaterials in medication delivery systems, aims to highlight the revolutionary potential of these smart biomaterials in transforming medicine delivery and enhancing patient outcomes by analyzing the most recent developments and obstacles.

LCST Thermo-Responsive System

The temperature at which a polymer solution becomes miscible below and splits into two different phases above is known as the lower critical solution temperature, or LCST. Several thermostable polymers, including poly(N-isopropylacrylamide) (PNIPAM), poly((2-dimethylamino)ethyl methacrylate) (PDMAEMA), and poly(propylene oxide), exhibit this LCST phase transition characteristic. These polymers also allow for the modulation of LCST by copolymerization with different monomers. (Shengyi Dong, 2016, Constantinos Tsitsilianis, 2020) As shown in Figure 1, under varying temperature circumstances, thermostable polymers coupled with hydrophobic blocks can form micelles and other aggregates. These amphiphilic materials, which change from thermostable polymers into hydrophilic blocks at temperatures below the copolymer's LCST, self-assemble into micelles-sized nanoparticles. Because both of these blocks are hydrophobic, these copolymers join together at temperatures higher than the material's LCST.

Hexanoate repeating units make up the synthetic polymer known as polycaprolactone (PCL). (Labet and Thielemans, 2009). This material is biocompatible, biodegradable, and presents good mechanical properties (Dash and Konkimalla, 2012), having a broad application in tissue engineering. (Zaroog, 2019) For instance, because they are thermostable and biodegradable, PNIPAM-PCL copolymers are appealing for use in biological applications .(Xuejuanwan, 2010). In 2017, the production and use of PNIPAM-PCL copolymers for drug administration were described by Dr. Patil's research group. The system's biocompatibility is enhanced by PCL's ability to biodegrade. These copolymers were synthesized using the atom transfer radical polymerization (ATRP) method, which is widely used to fabricate well-defined polymer structures. These PNIPAM-PCL copolymers can be self-assembled into micelles of approximately 100 nm in size. Pyrene, a hydrophobic molecule, was encapsulated in these micelles to study its release kinetics. The thermoresponsive behavior of PNIPAM-PCL showed a LCST of 32°C. When heated to 40°C, the micelles release their contents faster due to a phase transition at the LCST, which demonstrates its potential for drug controlled release applications. (Patil, 2017) In 2023, Chander Amgoth and his colleagues studied the controlled synthesis of thermally tunable porous films of (pNIPAM)-b-(PCL). They demonstrated that pNIPAM-b-PCL copolymers can self-assemble into porous films and respond to temperature changes. This thermosensitive behavior is characterized by an LCST at 32°C, above which the polymer undergoes a phase transition. It was shown that the porosity of the films can be adjusted by tuning the synthesis parameters, which in turn affects the drug release rate. In testing, the films demonstrated sustained release of encapsulated drugs, making them a promising candidate for controlled release drug delivery applications. (Chander, 2023)

Aside from poly(N-isopropylacrylamide) (PNIPAM), another cationic polymer that is pH-sensitive and water-soluble is poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA). The tertiary amine groups in the PDMAEMA backbone, as well as its thermo-oxidative degradation, are thought to be responsible for the PDMAEMA's thermostability. Recent research has also focused on thermo-oxidative deterioration. (Liulin, 2010) PDMAEMA-PCL copolymers can be synthesized through various methods, including ATRP of PDMAEMA using

PCL as the initiator. Additionally, a combination of ring-opening polymerization (ROP) and ATRP has also been reported for the synthesis of these copolymers. The properties of the copolymers, such as critical micellar concentration (CMC), hydrophobicity, and particle size, are strongly dependent on the length of the PCL segment. (Maria, 2021) Research by Hui Zou's group revealed that the PDMAEMA-PCL copolymer exhibits an LCST phase transition in aqueous solutions, with an LCST around 50-55 °C. This allows the copolymer to transform from a soluble to an insoluble state upon heating. Both copolymer composition and environmental condition can affect this transition. The composition is crucial; for instance, a higher hydrophobic content typically lowers the transition temperature. In acidic solutions, protonation of the amine groups in the PDMAEMA segment leads to smaller aggregates due to increased electrostatic repulsion. Conversely, at higher pH levels, the copolymers become more hydrophobic, resulting in larger particle formation. (Zou, 2020) Incorporating PVCL into the PDMAEMA-PCL copolymer enhances its hydrophobicity, further decreasing the LCST. This tunability allows the LCST to be adjusted to approach physiological temperatures, making the copolymer suitable for various biomedical applications, particularly in drug delivery. This feature is especially beneficial in cancer therapy, where the acidic environment of tumors can trigger the release of chemotherapeutic agents, and for inflammation-targeted therapies, where elevated temperatures at inflamed sites can activate drug release. (Yuan, 2023) PDMAEMA-PCL copolymers have been explored for various applications, particularly in the biomedical field. Jianhua Zhou's group used ring-opening polymerization (ROP) and reversible addition–fragmentation chain transfer (RAFT) polymerization to create star-shaped amphiphilic block copolymers, HPs-Star-PCL-b-PDMAEMA. These copolymers have a hydrophilic PDMAEMA arm encircling a hydrophobic, biodegradable poly(ε-caprolactone) (PCL) core that forms stable unimolecular micelles. They investigated the copolymers' size, stability, and responsiveness to environmental conditions, evaluating their drug delivery capabilities with aspirin as a model drug. The study demonstrated that the drug release rate could be effectively controlled by temperature. (Zhou, 2010) Additionally, related copolymers have been studied for their potential in co-delivering plasmid DNA and anticancer drugs, showing promise in biomedical applications. In 2011, Yuan et al. introduced a novel ABC 3-miktoarm star terpolymer that exhibits significant thermoresponsive properties, with its aggregate morphology in aqueous solutions changing with temperature. This terpolymer, consisting of hydrophilic MPEG, hydrophobic PCL, and thermosensitive polyphosphoester segments, forms micelles that transition from spherical to nano-rod shapes as the temperature exceeds the cloud point. This coil-to-globule transition, characterized by a volume phase transition temperature (VPTT), results in reduced viscosity and can be analyzed using turbidimetry and light scattering, highlighting the potential of this miktoarm terpolymer for intelligent, regulated drug delivery systems. (Yuan, 2011) In 2014, Yu-Lun Lo et al. conducted a study comparing the synthesis and characterization of a four-armed copolymer (Star-PCL-b-PDMAEMA) and its linear analogue (Linear-PCL-b-PDMAEMA) of similar composition. The study aimed to evaluate their ability to deliver a plasmid and doxorubicin, an anticancer drug. Both copolymers were designed with a hydrophobic block of polycaprolactone (PCL) and a thermoresponsive block of poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA) to self-assemble into micelles, known for its potential for gene delivery. Results indicated that the star-shaped copolymer exhibited enhanced complexation with DNA and improved encapsulation efficiency for doxorubicin compared to its linear counterpart. The star-shaped structure also facilitated sustained release profiles, potentially prolonging the therapeutic effect of the delivered agents. (Lo, 2014)

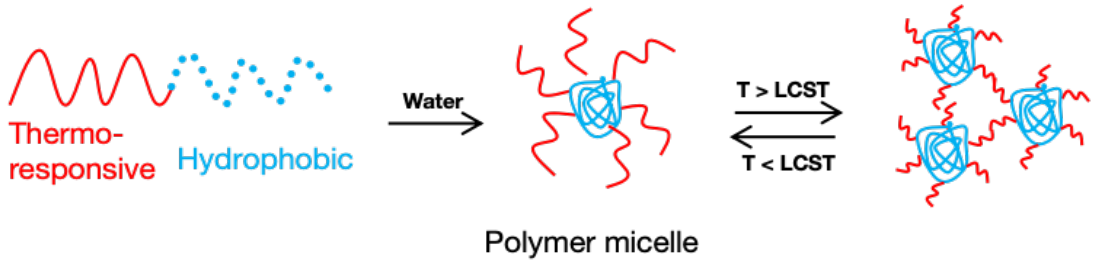

Figure 1. LCST behavior of thermo-responsive polymer with hydrophobic block

On the other hand, as shown in Figure 2, thermoresponsive polymers are capable of conjugation with hydrophilic polymers. For example, copolymerizing PNIPAM with a hydrophilic PEG block shows considerable potential. Polyethylene glycol (PEG) is a nontoxic, water-soluble polymer. Copolymerizing PNIPAM with PEG effectively alters the hydrogels' characteristics, including hydrophilic/hydrophobic balance, mechanical strength, biocompatibility, and biodegradability. Incorporating PEG into the PNIPAM network enhances mechanical strength and minimizes the initial burst effect of drug release. PNIPAM-PEG hydrogels also exhibit temperature-responsive behavior, with reversible volume changes and sol-gel phase transitions occurring in response to temperature variations around the lower critical solution temperature (LCST). This temperature-responsive property allows for easy drug encapsulation in the hydrogel at low temperatures and controlled, sustained drug release when the temperature rises over the LCST. The PNIPAM-PEG composite hydrogels can overcome the limitations of traditional drug delivery methods by increasing drug solubility, enabling prolonged drug release, and decreasing adverse effects. The thermoresponsive nature of PNIPAM-PEG hydrogels also makes them promising candidates for tissue engineering and wound dressing applications. (Xiaomin Xu, 2020) Addressing these dual challenges is complex, but Cai et al. developed a solution termed Shear-Thinning Hydrogel for Injectable Encapsulation and Long-Term Delivery (SHIELD). This PNIPAM-based hydrogel comprises two components: an 8-arm polyethylene glycol (PEG) with one arm attached to PNIPAM and others to proline-rich peptide sequences, and a linear protein copolymer with CC43 WW domains and RGD cell-binding domains. SHIELD leverages a dual physical crosslinking process: initially, peptide-PEG copolymers and recombinant proteins form a weak, ex vivo network through molecular recognition, providing mechanical protection during injection. Subsequently, in vivo, PNIPAM's thermal phase transition induces further crosslinking, strengthening the matrix to support long-term cell survival. This composite hydrogel significantly enhances transplanted cell retention, offering promising advancements in regenerative medicine therapies and drug delivery system study. (Cai, 2016)

Polyacrylic acid (PAA) is a polymer characterized by its non-toxicity, compatibility with living organisms, and natural biodegradability, which has garnered significant attention from researchers. PAA nano-derivatives can be obtained by chemical modification of carboxyl groups with superior chemical properties in comparison to unmodified PAA. (Haasan, 2022) In a study conducted in 2011, Xiong and his team examined the responses of the diblock polyampholyte PDMAEMA-b-PAA to thermo environmental stimuli in aqueous solutions. The research revealed that PDMAEMA-b-PAA exhibits temperature sensitivity, demonstrated by its behavior at lower critical solution temperatures (LCST). Below its LCST, the polyampholyte maintains solubility due to hydrogen bonding between the polymer and water molecules. However, an increase in temperature beyond the LCST disrupts these hydrogen bonds, leading to the collapse of the polymer chains and subsequent precipitation. This thermo-responsive behavior presents numerous applications, such as drug delivery systems that release their payloads in response to specific temperature conditions, biological sensing technologies that detect certain biomarkers through changes in polymer solubility, and the creation of materials that respond to environmental variations. In summary, this research emphasizes the potential of PDMAEMA-b-PAA to develop smart materials capable of adapting to their surroundings. (Xiong, 2011)

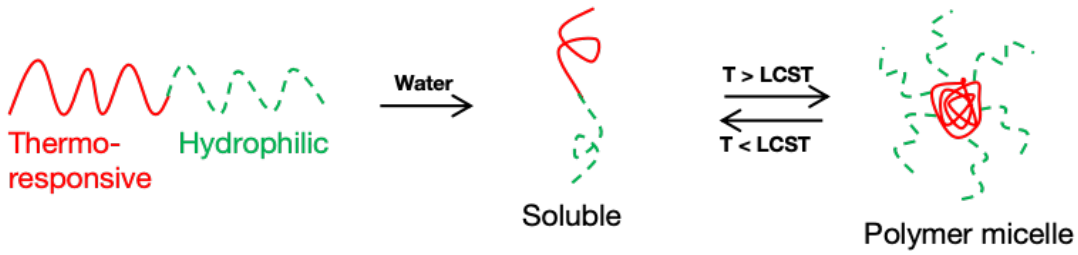

Figure 2. LCST behavior of thermo-responsive polymer with hydrophilic block

UCST Thermo-Responsive System

There is an inverse phenomenon of lower critical solution temperature (LCST) behaviour called upper critical solution temperature (UCST) behavior. UCST behavior is a characteristic of certain thermoresponsive polymers where the polymer solution remains homogeneous above a specific temperature but phase-separates into two distinct phases below this temperature. (Beatriz 2016) The UCST property can be tailored by copolymerization with other monomers, which affects their solubility and aggregation dynamics. Also, UCST behavior is influenced by the interactions between polymer chains and the solvent. Above the UCST, the polymer-solvent interactions are favorable enough to keep the solution mixed and homogeneous. Below the UCST, polymer-polymer interactions dominate, causing the polymer to become less soluble and leading to phase separation. This transition can be tuned by various factors, including polymer concentration, molecular weight, and the presence of additives such as salts. For instance, poly(acrylic acid) demonstrates UCST behavior due to hydrogen bonding interactions that become less favorable with decreasing temperature, leading to phase separation.(Sharker et al. 2019) Figure 3 illustrates how thermoresponsive polymers conjugated with hydrophobic blocks can form micelles and other aggregates under varying temperature conditions. Above the UCST, these copolymers aggregate due to the hydrophobic interactions between the blocks, facilitating the formation of larger structures. Conversely, below the UCST, the amphiphilic nature of the polymer favors the self-assembly of hydrophilic blocks into smaller nanoparticles, such as micelles, within the solvent.

Poly(N-acryloyl glycinamide)(PNAGA) is the thermoresponsive polymer with phase transition behavior characterized. For instance, PNAGA-co-NAS is a biodegradable and biocompatible copolymer that exhibits UCST behavior. PNAGA can form strong hydrogen bonds through the dual amide motifs in its side chain, allowing the polymer to exhibit gelation behavior and an upper critical solution temperature (UCST) property. To improve the UCST tunability and bio-interfacial adhesion of PNAGA nanoparticles, researchers developed a reactive hydrogen-bond-type P(NAGA-co-NAS) copolymer via reversible addition-fragmentation chain transfer polymerization. This copolymer exhibited a tunable UCST over a broad temperature range, showing a thermo-reversible transition between nanoparticles (PNPs) and soluble chains. The PNPs effectively bonded proteins into nano-biohybrids while preserving the proteins' secondary structure. Additionally, they demonstrated good adhesion to cell membranes and significantly inhibited cell-specific propagation. These features suggest broad prospects for P(NAGA-co-NAS) nanoparticles in biosensors, protein delivery, cell surface decoration, and cell-specific function regulation. (Tian, 2023) The study by Boustta et al. explores the potential of UCST-based thermoresponsive hydrogels for sustained local drug delivery. These hydrogels, made from neutral Poly(N-acryloyl glycinamide), exhibit a temperature-dependent gel-sol transition, with a transition temperature just above body temperature. This feature enables easy injection and rapid transformation into a gel upon contact with tissues, allowing for controlled and prolonged drug release. The hydrogels showed effective diffusion-controlled release profiles, achieving complete release within 2 to 3 weeks. In vitro tests with various model compounds, including dyes and albumin, and in vivo tests with methylene blue in mice, demonstrated a sustained release for up to 52 hours, significantly longer than a polymer-free control solution. These results highlight the hydrogels' promise for loco-regional drug administration. (Boustta 2014)

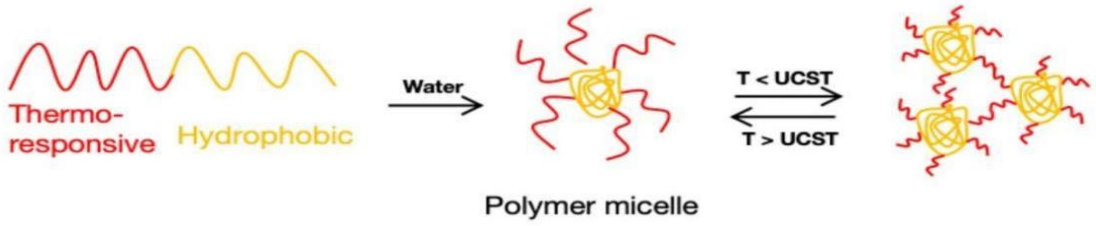

Figure 3. UCST behavior of thermo-responsive polymer with hydrophobic block

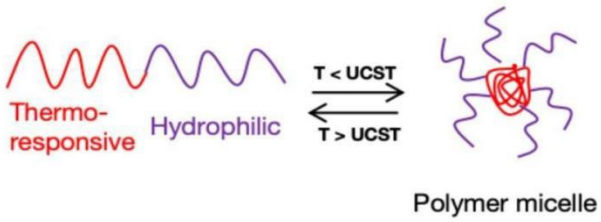

Figure 4. UCST behavior of thermo-responsive polymer with hydrophilic block

As depicted in Figure 4, when thermoresponsive polymers conjugated with hydrophilic blocks are cooled below the UCST, the hydrophilic properties of the blocks dominate, causing the polymers to aggregate and phase-separate, forming distinct structures such as micelles or precipitates. When they are heated above their UCST, they remain soluble and form uniform solutions. In this case, PNAGA-HA is a great example of a hydrophilic copolymer. A study by Boustta's group reports the synthesis and characterization of new thermoresponsive hydrogels based on copolymers of hyaluronic acid (HA) and poly(N-acryloyl glycinamide) (PNAGA) using a one-pot free-radical polymerization approach. The resulting HA-PNAGA copolymers formed UCST-type hydrogels, and their properties were found to be dependent on the feed composition and copolymer concentration. The UCST-type transition behavior was observed for all the different feed compositions of HA and NAGA that were polymerized. However, the observation of the UCST-type phase transitions alone did not conclusively prove the formation of the expected comb-like copolymer structure, as mixtures of the individual HA and PNAGA homopolymers also exhibited gel-sol transitions. Further analytical techniques were required to demonstrate the grafting of the PNAGA segments directly onto the HA backbone to form the desired comb-like copolymer architecture. The drug delivery potential of the newly developed HA-PNAGA hydrogels was investigated using Prednisolone, a synthetic corticosteroid commonly used to treat inflammation and autoimmune conditions, as a model drug. The study demonstrated that these thermoresponsive hydrogels could sustain the release of Prednisolone over extended periods, highlighting their potential as versatile, degradable, and injectable drug delivery systems. (Boustta 2020)

LCST and UCST Combined Thermo-Responsive System

Figure 5. LCST/UCST behavior of thermo-responsive polymers.

A significant development in smart polymer design is a combination thermo-responsive system with both lower critical solution temperature (LCST) and upper critical solution temperature (UCST). This system may combine both LCST and UCST characteristics into a single framework by going through phase transitions in response to temperature variations. This integration marks a significant breakthrough, offering enhanced functionality and versatility for various applications, especially in biomedical technologies where environmental responsiveness is key. Ongoing research and development in this area hold the potential to reveal innovative solutions that harness the unique properties of these combined thermo-responsive materials. (Sun, 2018) For example, as shown in Figure 5, at temperatures below UCST of PNAGA, the PNAGA segments are extended, while the PNIPAM segments remain aggregated, forming micelle-like structures with PNAGA forming the corona and PNIPAM the core. Upon heating above the LCST of

PNIPAM, the PNIPAM segments become extended, while PNAGA segments collapse, leading to the inversion of the micelle structure. This thermoresponsive behavior allows the system to transition between two distinct conformations, potentially enabling controlled drug release and other applications.

A similar study "Triple Hydrophilic UCST–LCST Block Copolymers" by Mäkinen et al., published in Macromolecules, explores the synthesis and properties of dual thermoresponsive ABC-type triblock copolymers with PNAGA and PNIPAM that exhibit both upper critical solution temperature (UCST) and lower critical solution temperature (LCST) behaviors. (Mäkinen, 2016) The study describes the production of these block copolymers and their temperature-sensitive micellar self-assembly, demonstrating that block composition may be changed to modify the thermoresponsive behavior of the micelles and influence their size and temperature sensitivity. Their thermal characteristics and structural integrity are verified by characterization utilizing methods such as differential scanning calorimetry (DSC) and nuclear magnetic resonance (NMR). The study highlights their potential for smart drug delivery systems, where precise temperature control can trigger drug release, and suggests further customization of these materials for specific biomedical applications through tailored synthesis. A study from Gang Wu's team focused on the synthesis and properties of a copolymer called PVA-g-PPDO, which combines poly(p-dioxanone) with poly(vinyl alcohol). The scientists used a three-step "grafting onto" technique to produce a well-defined, biodegradable, and biocompatible structure. These copolymers are distinguished by their special thermoresponsive activity, which allows them to display reactions at both the UCST and LCST. The thermoresponsive behavior of the graft may be changed from LCST to UCST by varying its chain length. Depending on the esterification step's molar feed ratios and degree of polymerization (Dp), the transition temperature can range from 30 to 80 °C. The team used transmittance measurements to assess the thermoresponsive characteristics and dynamic light scattering (DLS) to study the solution properties and self-assembly of the copolymers under different temperature and concentration conditions. Because the copolymers may be structurally and environmentally modified to suit specific purposes, their promise as drug delivery systems is highlighted by their capacity to manage thermoresponsiveness and self-assembly. This work paves the path for further research and development in this area and provides new insights into the synthesis of copolymers with switchable thermoresponsive properties. It also adds important knowledge to the design of multifunctional polymers for biological applications. (Wu, 2011)

Using a three-step "grafting onto" technique, Yicheng Zhu's group has conducted another study that investigates the synthesis and properties of a poly(p-dioxanone)-grafted poly(vinyl alcohol) (PVA-g-PPDO) copolymer. This approach enables precise control over the copolymer's structure and its thermoresponsive properties. By only varying the graft chain length, the copolymers may change their thermoresponsivity from LCST to UCST. The degree of polymerization (Dp), molar feed ratios during the last esterification stage, the hydrophobic/hydrophilic ratios, and the adjustable structures of the copolymers all affect this thermo-response's adaptability. The results suggest that these copolymers can self-assemble and be regulated through structural and temperature changes, highlighting their potential for applications in drug delivery systems and responsive materials. The two studies differ in their focus and details about copolymer synthesis and properties. Research from Gang Wu details the creation of star-shaped amphiphilic block copolymers using ROP and RAFT polymerization, highlighting their stable micelle formation and temperature-controlled drug release capabilities with aspirin. In contrast, Yicheng Zhu describes a graft copolymer synthesized via a "grafting onto" method, featuring both LCST and UCST thermoresponsivity, which can be tuned by adjusting the graft chain length. It emphasizes the copolymer's versatility, with a focus on precise control over structure and thermoresponsive behavior. (Zhu, 2016)

Dual Stimuli-Responsive System

Besides temperature-based responsive biomaterials, many other responsive polymers focus on pH, light, temperature, or oxidative stress. Nonetheless, a large body of research has been done in the field of numerous stimuli for biological applications. Dual stimuli-responsive systems are one type of system that has gained a lot of traction in recent years due to its ability to respond simultaneously to two different environmental triggers, providing more functionality and

control. These systems may be made to display certain behaviors in response to combinations of outside inputs, allowing for more intricate reactions appropriate for sophisticated uses including biosensing, tissue engineering, and targeted drug administration. By adjusting medication release patterns, these devices enhance therapeutic efficacy while reducing adverse effects. For example, a polymer loaded with a medicine might react to temperature and pH, guaranteeing the release of the therapeutic agent only in particular conditions, such as tumors or inflammatory tissues, which frequently exhibit changes in both parameters. Moreover, materials that respond to two stimuli simultaneously can have synergistic effects that improve the overall efficacy of biological applications and increase design diversity. (Ahiabu, 2017) In 2017, stubbs's group investigated the control of pH- and temperature-responsive behavior of mPEG-b-PDMAEMA copolymers by varying their composition. PDMAEMA-PEG copolymers exhibit a lower critical solution temperature (LCST) phase transition behavior in aqueous solutions. They focused on how the ratio of mPEG (polyethylene glycol) to PDMAEMA (poly(N, N-dimethylaminoethyl methacrylate)) affects the critical solution temperature (LCST) and pH-responsive properties. The study revealed that by altering the polymer composition, specifically the mPEG ratio, significant changes in the LCST and pH responsiveness could be achieved. This demonstrates that higher PDMAEMA content enhances the copolymer's hydrophobic interactions, thus decreasing the LCST. These copolymers can be precisely manipulated to control the LCST and pH-responsive behavior, which makes them ideal for a wide range of applications, such as drug delivery systems, responsive coatings, and smart materials that respond to temperature changes in the environment. (Stubbs, 2017) By responding differently to temperature and pH, copolymers of polycaprolactone (PCL), acrylic acid (AA), and PNIPAM enhance functionality. PNIPAM, with a lower critical solution temperature (LCST) of around 32°C, transitions from hydrophilic to hydrophobic states upon heating. The addition of AA affects the polymer's solubility because its carboxylic acid groups increase pH sensitivity. These systems are typically synthesized via free-radical polymerization to create diblock or triblock copolymers, with the LCST being tunable by adjusting the monomer ratios. In drug delivery applications, these dual-responsive systems facilitate controlled release by dissolving at room temperature and targeting pH-specific environments, such as acidic tumor tissues, thereby optimizing therapeutic efficacy and minimizing side effects. The interaction between LCST and pH responsiveness is crucial, as varying pH levels can alter the polymer's solubility and LCST, enabling precise modulation of drug release profiles for targeted therapies. (Lanzalaco, 2017)

Aristeidis's study in 2021 examined how changing the polymer composition might affect the pH and temperature-responsive behavior of mPEG-b-PDMAEMA copolymers. After adjusting the lengths of the mPEG and PDMAEMA blocks, the researchers can precisely tune the copolymers' LCST, which gives them the ability to control the copolymers' pH-responsiveness and thermal stability. It was discovered that while lengthening the mPEG block increased the LCST, lengthening the PDMAEMA block lowered the LCST. This is due to the fact that longer mPEG segments increase hydrophilicity, raising the LCST, whereas longer PDMAEMA segments promote hydrophobic interactions, reducing the LCST. The investigation also revealed that the copolymers have reversible solubility in water, with distinct temperature-dependent shifts from soluble to insoluble states. Copolymers underwent a reversible transition, disintegrating again when cooled. Additionally, the pH of the solution had an impact on the LCST, which decreased at lower pH levels because PDMAEMA becomes more hydrophilic when it is protonated. These materials' customizable temperature and pH responses point to possible uses in drug and gene delivery, as well as in the creation of stimuli-responsive hydrogels and other materials for industrial and medicinal applications. (Aristeidis, 2021)

In order to provide regulated drug administration, Kokila Thirupathi's work investigates a dual stimuli-responsive hydrogel, namely a PNIPAm-co-Polyacrylamide (PAAm) hydrogel modified with melamine and glutaraldehyde. Because of its pH and thermoresponsive characteristics, this hydrogel enables tailored medication release in response to changes in the surrounding environment. Characterization confirmed its structural and physicochemical attributes and drug release experiments demonstrated significant pH-sensitive release efficiency, particularly for Curcumin (Cur). Structural studies confirmed the successful formation of the PNIPAm-co-PAAm-Mela hydrogel and its unique phase transition properties, enhancing drug delivery capabilities. Cytocompatibility evaluations indicated favorable compatibility for therapeutic applications, suggesting promising future applications in targeted cancer therapies and personalized medicine. (Thirupathi, 2022) The study by Cheng Wang explores advancements in photo-thermo

coupled responsive hydrogels, focusing on their design and applications in drug delivery. The researchers developed hydrogels using amphiphilic triblock copolymers (PNIPAM-b-PNAM-b-PNBOC) that respond to both light and temperature changes. These hydrogels can deliver hydrophilic gemcitabine (GCT) and hydrophobic doxorubicin (DOX) by self-assembling into micelles with photosensitive cores, hydrophilic shells, and thermoresponsive outer layers. The hydrogels, which are physically cross-linked into nanoparticles, exhibit tunable gel-to-sol transitions in response to temperature or UV light, enabling controlled drug release. This approach combines natural and synthetic polymers to enhance biocompatibility and responsiveness, making these hydrogels suitable for targeted drug delivery. The study highlights their potential in various biomedical applications and suggests future developments could include more sophisticated hydrogels for regenerative medicine, cancer therapy, and diagnostic tools, paving the way for innovative treatment strategies. (Wang, 2017)

Conclusion

In conclusion, biodegradable thermo-responsive polymers represent a promising innovation within the realm of drug delivery systems. The distinctive properties of LCST and UCST thermoresponsive mechanisms enable the precise control of drug release in response to environmental stimuli, facilitating targeted therapeutic interventions. Their biodegradability ensures reduced toxicity and promotes enhanced biocompatibility, which are critical for clinical applications. Furthermore, the integration of these materials with emerging technologies, such as nanotechnology and biotechnology, holds great promise for creating multifunctional drug delivery platforms that can address complex medical challenges. The transformative impact of these materials underscores their significant potential in advancing biomedical applications and improving treatment outcomes in various medical fields. As research progresses, biodegradable thermo-responsive polymers will play a crucial role in revolutionizing personalized medicine, enhancing patient care, and optimizing therapeutic efficacy. Looking ahead, ongoing research should focus on optimizing the synthesis and functionalization of these polymers to further enhance their performance, paving the way for a new class of advanced drug delivery systems that are not only effective but also tailored to meet the specific needs of patients, such as cancer.

Acknowledgment

I would like to thank my advisor Dr. Jingya Qin for helping me with this project.

Reference

1. Wang, Yucai, et al. “Stimuli-Responsive Materials for Controlled Release of Theranostic Agents.” *Advanced Functional Materials*, vol. 24, no. 27, Apr. 2014, pp. 4206–20. https://doi.org/10.1002/adfm.201400279.

2. Kim, Young-Jin, and Yukiko T. Matsunaga. “Thermo-responsive polymers and their application as smart biomaterials.” Journal of Materials Chemistry B, vol. 5, no. 23, Jan. 2017, pp. 4307–21. https://doi.org/10.1039/c7tb00157f.

3. Lanzalaco, Sonia, and Elaine Armelin. “Poly(N-isopropylacrylamide) and Copolymers: A Review on Recent Progresses in Biomedical Applications.” Gels, vol. 3, no. 4, Oct. 2017, p. 36. https://doi.org/10.3390/gels3040036.

4. Xu, Ziyang, and Wenguang Liu. “Poly(N-acryloyl glycinamide): a fascinating polymer that exhibits a range of properties from UCST to high-strength hydrogels.” Chemical Communications, vol. 54, no. 75, Jan. 2018, pp. 10540–53. https://doi.org/10.1039/c8cc04614j.

5. Chatterjee, Sudipta, and Patrick Chi-Leung Hui. “Review of Applications and Future Prospects of Stimuli-Responsive Hydrogel Based on Thermo-Responsive Biopolymers in Drug Delivery Systems.” Polymers, vol. 13, no. 13, June 2021, p. 2086. https://doi.org/10.3390/polym13132086.

6. Gandhi, Arijit, et al. “Studies on thermoresponsive polymers: Phase behaviour, drug delivery and biomedical applications.” Asian Journal of Pharmaceutical Sciences, vol. 10, no. 2, Apr. 2015, pp. 99–107. https://doi.org/10.1016/j.ajps.2014.08.010.

7. Dong, Shengyi, et al. “Lower critical solution temperature (LCST) phase behaviour of an ionic liquid and its control by supramolecular host–guest interactions.” Chemical Communications, vol. 52, no. 51, Jan. 2016, pp. 7970–73. https://doi.org/10.1039/c6cc02838a.

8. Pasparakis, George, and Constantinos Tsitsilianis. “LCST polymers: Thermoresponsive nanostructured assemblies towards bioapplications.” Polymer, vol. 211, Dec. 2020, p. 123146. https://doi.org/10.1016/j.polymer.2020.123146.

9. Labet, Marianne, and Wim Thielemans. “Synthesis of polycaprolactone: a review.” Chemical Society Reviews, vol. 38, no. 12, Jan. 2009, p. 3484. https://doi.org/10.1039/b820162p.

10. Dash, Tapan K., and V. Badireenath Konkimalla. “Poly-ϵ-caprolactone based formulations for drug delivery and tissue engineering: A review.” Journal of Controlled Release, vol. 158, no. 1, Feb. 2012, pp. 15–33. https://doi.org/10.1016/j.jconrel.2011.09.064.

11. Zaroog, Omar S., et al. “Biomaterials for Bone Tissue Engineering: Properties and Applications.” Elsevier eBooks, 2019, pp. 335–47. https://doi.org/10.1016/b978-0-12-803581-8.11394-3.

12. Wan, Xuejuan, et al. “Synthesis of Amphiphilic Tadpole-Shaped Linear-Cyclic Diblock Copolymers via Ring-Opening Polymerization Directly Initiating from Cyclic Precursors and Their Application as Drug Nanocarriers.” Biomacromolecules, vol. 12, no. 4, Feb. 2011, pp. 1146–54. https://doi.org/10.1021/bm101463d.

13. Amgoth, Chander, et al. “Controlled synthesis of thermosensitive tunable porous film of (pNIPAM)-b-(PCL) copolymer for sustain drug delivery.” Journal of Applied Polymer Science, vol. 140, no. 20, Mar. 2023, https://doi.org/10.1002/app.53854.

14. Lin, Liu. “Synthesis of Amphiphilic Block Copolymer PCL-b-PDMAEMA by the Combination of Enzymatic-promoting Polymerization with ATRP and Its Self-assembly Behavior.” Gaodeng Xuexiao Huaxue Xuebao, Jan. 2010, en.cnki.com.cn/Article_en/CJFDTotal-GDXH201012041.htm.

15. Kupczak, Maria, et al. “The Influence of Polymer Composition on the Hydrolytic and Enzymatic Degradation of Polyesters and Their Block Copolymers with PDMAEMA.” Materials, vol. 14, no. 13, June 2021, p. 3636. https://doi.org/10.3390/ma14133636.

16. Zou, Hui, et al. “Thermo- and redox-responsive dumbbell-shaped copolymers: from structure design to the LCST–UCST transition.” Polymer Chemistry, vol. 11, no. 4, Jan. 2020, pp. 830–42. https://doi.org/10.1039/c9py01566c.

17. Yuan, Yichun, et al. “Thermoresponsive polymers with LCST transition: synthesis, characterization, and their impact on biomedical frontiers.” RSC Applied Polymers, vol. 1, no. 2, Jan. 2023, pp. 158–89. https://doi.org/10.1039/d3lp00114h.

18. Zhou, Jianhua, et al. “Temperature- and pH-responsive star amphiphilic block copolymer prepared by a combining strategy of ring-opening polymerization and reversible addition–fragmentation transfer polymerization.” European Polymer Journal, vol. 46, no. 6, June 2010, pp. 1288–98. https://doi.org/10.1016/j.eurpolymj.2010.03.004.

19. Yuan, You-Yong, and Jun Wang. “Temperature-induced morphological change of ABC 3-miktoarm star terpolymer assemblies in aqueous solution.” Colloids and Surfaces B Biointerfaces, vol. 85, no. 1, June 2011, pp. 81–85. https://doi.org/10.1016/j.colsurfb.2010.10.044.

20. Lo, Yu-Lun, et al. “Synthesis and characterization of S-PCL-PDMAEMA for co-delivery of pDNA and DOX.” RSC Advances, vol. 4, no. 22, Jan. 2014, pp. 11089–98. https://doi.org/10.1039/c3ra46914j.

21. Xu, Xiaomin, et al. “Poly(N-isopropylacrylamide)-Based Thermoresponsive Composite Hydrogels for Biomedical Applications.” Polymers, vol. 12, no. 3, Mar. 2020, p. 580. https://doi.org/10.3390/polym12030580.

22. Cai, Lei, et al. “Regulating Stem Cell Secretome Using Injectable Hydrogels with In Situ Network Formation.” Advanced Healthcare Materials, vol. 5, no. 21, Oct. 2016, pp. 2758–64. https://doi.org/10.1002/adhm.201600497.

23. Arkaban, Hassan, et al. “Polyacrylic Acid Nanoplatforms: Antimicrobial, Tissue Engineering, and Cancer Theranostic Applications.” Polymers, vol. 14, no. 6, Mar. 2022, p. 1259. https://doi.org/10.3390/polym14061259.

24. Xiong, Zhiying, et al. “Dual-stimuli responsive behaviors of diblock polyampholyte PDMAEMA-b-PAA in aqueous solution.” Journal of Colloid and Interface Science, vol. 356, no. 2, Apr. 2011, pp. 557–65. https://doi.org/10.1016/j.jcis.2011.01.067.

25. Pineda-Contreras, Beatriz Amanda. Basic Studies of UCST Polymers in Water and their Processing as Films and Fibers. 1 Jan. 2017, epub.uni-bayreuth.de/3328.

26. Sharker, Komol Kanta, et al. “Upper Critical Solution Temperature (UCST) Behavior of Polystyrene-Based Polyampholytes in Aqueous Solution.” Polymers, vol. 11, no. 2, Feb. 2019, p. 265. https://doi.org/10.3390/polym11020265.

27. Tian, Yueyi, et al. “Poly(N-acryloyl glycinamide-co-N-acryloxysuccinimide) Nanoparticles: Tunable Thermo-Responsiveness and Improved Bio-Interfacial Adhesion for Cell Function Regulation.” ACS Applied Materials & Interfaces, vol. 15, no. 6, Feb. 2023, pp. 7867–77. https://doi.org/10.1021/acsami.2c22267.

28. Boustta, Mahfoud, et al. “Versatile UCST-based thermoresponsive hydrogels for loco-regional sustained drug delivery.” Journal of Controlled Release, vol. 174, Jan. 2014, pp. 1–6. https://doi.org/10.1016/j.jconrel.2013.10.040.

29. Boustta, Mahfoud, and Michel Vert. “Hyaluronic Acid-Poly(N-acryloyl glycinamide) Copolymers as Sources of Degradable Thermoresponsive Hydrogels for Therapy.” Gels, vol. 6, no. 4, Nov. 2020, p. 42. https://doi.org/10.3390/gels6040042.

30. Sun, Hui, et al. “Multi-responsive hydrogels with UCST- and LCST-induced shrinking and controlled release behaviors of rhodamine B.” Materials Science and Engineering C, vol. 82, Jan. 2018, pp. 284–90. https://doi.org/10.1016/j.msec.2017.08.067.

31. Mäkinen, Lauri, et al. “Triple Hydrophilic UCST–LCST Block Copolymers.” Macromolecules, vol. 49, no. 3, Jan. 2016, pp. 986–93. https://doi.org/10.1021/acs.macromol.5b02543.

32. Wu, Gang, et al. “Well-Defined Amphiphilic Biodegradable Comb-Like Graft Copolymers: Their Unique Architecture-Determined LCST and UCST Thermoresponsivity.” Macromolecules, vol. 44, no. 4, Jan. 2011, pp. 999–1008. https://doi.org/10.1021/ma102588k.

33. Zhu, Yicheng, et al. “Design of Thermoresponsive Polymers with Aqueous LCST, UCST, or Both: Modification of a Reactive Poly(2-vinyl-4,4-dimethylazlactone) Scaffold.” Macromolecules, vol. 49, no. 2, Jan. 2016, pp. 672–80. https://doi.org/10.1021/acs.macromol.5b02056.

34. Ahiabu, Andrews, and Michael J. Serpe. “Rapidly Responding pH- and Temperature-Responsive Poly (N-Isopropylacrylamide)-Based Microgels and Assemblies.” ACS Omega, vol. 2, no. 5, May 2017, pp. 1769–77. https://doi.org/10.1021/acsomega.7b00103.

35. Stubbs, Elizabeth, et al. “Control of pH- and temperature-responsive behavior of mPEG-b-PDMAEMA copolymers through polymer composition.” Journal of Macromolecular Science Part A, vol. 54, no. 4, Mar. 2017, pp. 228–35. https://doi.org/10.1080/10601325.2017.1282694.

36. Papagiannopoulos, Aristeidis, et al. “Length-scale dependence of pH- and temperature-response of PDMAEMA-b-PHPMA block copolymer self-assemblies in aqueous solutions.” Polymer, vol. 239, Jan. 2022, p. 124428. https://doi.org/10.1016/j.polymer.2021.124428.

37. Thirupathi, Kokila, et al. “pH and Thermoresponsive PNIPAm-co-Polyacrylamide Hydrogel for Dual Stimuli-Responsive Controlled Drug Delivery.” Polymers, vol. 15, no. 1, Dec. 2022, p. 167. https://doi.org/10.3390/polym15010167.

38. Wang, Cheng, et al. “Photo- and thermo-responsive multicompartment hydrogels for synergistic delivery of gemcitabine and doxorubicin.” Journal of Controlled Release, vol. 259, Aug. 2017, pp. 149–59. https://doi.org/10.1016/j.jconrel.2016.11.007.