THERMORESPONSIVE SMART POLYMERS AND THEIR APPLICATIONS IN THE BIOMEDICAL FIELD

Abstract

Thermo-responsive polymers have gained significant attention in the realm of biological applications owing to their distinctive capacity to undergo reversible phase transitions in reaction to temperature variations. These polymers demonstrate a distinct shift from a water-loving (hydrophilic) to a water-repelling (hydrophobic) state across a limited temperature range. As a result, they are highly suitable for precise administration of drugs and use in tissue engineering. The chapter begins with providing insights of the smart polymers and their different categories based their sensitivity towards different stimuli, followed by elucidation of fundamental principles and working mechanism of thermoresponsive and the significance of their lower critical solution temperature (LCST) and upper critical solution temperature (UCST) transitions, showing their potential in the biomedical realm, spanning a wide spectrum including drug delivery systems, gene delivery transfection, and tissue engineering. Moreover, future prospects and emerging trends for utilization of thermoresponsive smart polymers are emphasized along with the ongoing research and breakthroughs in this rapidly evolving field and serves as an invaluable resource for researchers, scientist, and healthcare professionals to harness burgeoning role and potential of these materials in pursuit of advanced medical solutions.

Keywords: Thermoresponsive polymers, LCST, UCST, Biological Applications.

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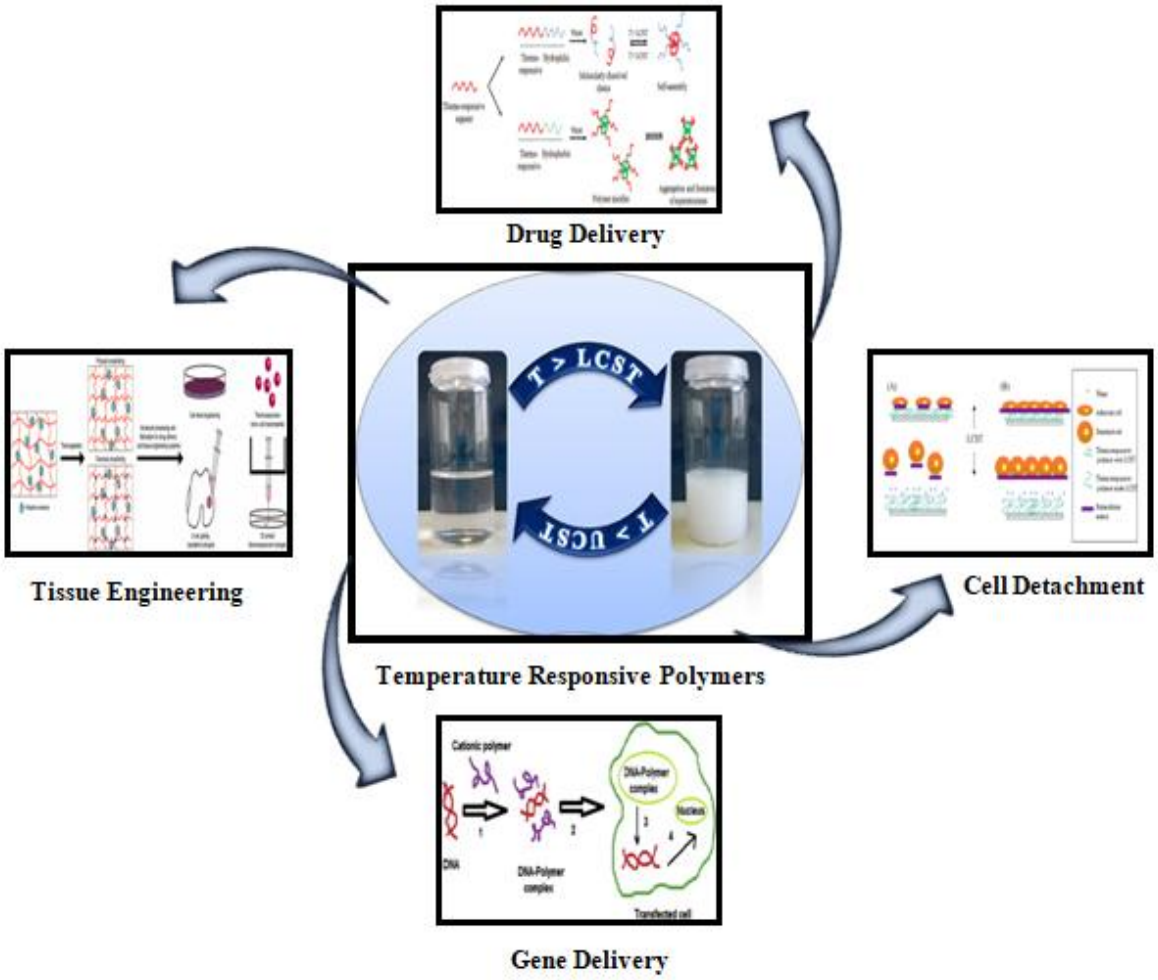
Graphical Abstract



I. INTRODUCTION

"Life is polymeric in its essence" as proteins, carbohydrates and nucleic acids are all biopolymers where it's been extensively used polymers both as structural and functional parts of complicated cell machinery. As biopolymers exhibit high nonlinearity and extra sensitivity towards external stimuli and coordinated interaction of it suggested the idea to mimic the cooperative behavior in synthetic systems. From the last two to three decades, the need of designing advanced intelligent material which can fit in the modern requirement criteria of material desired by the advanced industrial sectors has exponentially increased the interest of the scientific community for the development of smart polymers [1,2]. Where all the stimuli sensitive polymers or environmentally responsive polymers are defined as the smart or intelligent polymers. Dagani et. al. in 1995 coined the name smart polymers for their similarity to biopolymers. Later, with advancement in science and technology, several other synthetic polymers are designed to mimic the naturally abundant biopolymers by a variety of functionalization's in their physicochemical properties and structures [3]. In scientific literature, terms like intelligent polymers, stimuli responsive polymers and environmental sensitive polymers are used interchangeably for smart materials [4].

Smart polymers exhibit a remarkably responsive nature to even the most subtle alterations, which may arise from external factors like temperature, light, electric and magnetic fields, mechanical strain, and chemical modifications such as variations in pH, ionic strength and the presence of reactive metabolites in their surroundings. This exceptional sensitivity makes them suitable for a diverse array of applications [5]. These factors have the potential to induce alterations in the macroscopic properties of the polymer, such as modifications in its structure, shape, solubility, surface characteristics, formation of molecular assemblies, and the transition between sol and gel states. These changes are dependent on the physical state of the polymer chain. One of the most intriguing characteristics of intelligent polymers is their capacity to undergo a reversible transition and return to their original state when the stimulus is substituted or eliminated [6]. Synthetic polymers possess the inherent capability to undergo functionalization through two distinct approaches: pre-polymerization and post-polymerization techniques. These methods involve the integration of functional molecules, such as biological receptors and sensory units, into the original structures of the polymers [7]. These additives facilitate a diverse array of potential outcomes in relation to the reduction of chemical structures of polymers, their architectures, arrangement, and so forth. The integration of polymer modifications results in the emergence of multiple applications for these intelligent polymers in diverse areas such as biomaterial separation, drug delivery, biocatalyst development, and biomimetic actuators. The alterations in surfaces with switchable hydrophobic and hydrophilic properties are driven by various stimuli. For instance, the process of neutralizing charge groups can occur through either a change in pH or the introduction of a polymer with an opposite charge. Additionally, as the temperature or ionic strength increases, the efficiency of hydrogen bonding can change, and hydrogels that have interpenetrating polymer networks may collapse. The user's text does not contain any information to rewrite in a scientific manner. The occurrence of these transitions can be attributed to the equilibrium between hydrophilicity and hydrophobicity in the molecular composition of the polymer. Notably, the highly nonlinear behaviors of smart polymers have primarily been observed in aqueous environments, with occasional observations in other solvents and polyblends. In the vicinity of the transition conditions, linear and solubilized smart macromolecules have the ability to undergo a

transition from a single-phase state to a two-phase state, resulting in the formation of reversible sol-gel states. A highly intelligent crosslinked network experiences chain recognition during transition conditions, wherein the network undergoes a transformation from a compacted to an expanded state. Smart surfaces exhibit the ability to alter their affinity for water based on the presence of responsive interfaces that provide a stimulus. The aforementioned modifications are employed in the development of intelligent devices for various applications, such as minimally invasive injectable systems, pulsatile drug delivery systems, or novel substrates for cell culture or tissue engineering. Smart surfaces change their hydrophilicity as a function of stimulus-providing responsive interfaces. The above-mentioned changes are used in designing smart devices for multiple applications like minimally invasive injectable systems, pulsatile drug delivery systems, or new substrates for cell culture or tissue engineering. Smart polymers are used as substrates in tissue engineering applications for regulating the cell behavior in response to external factors. Tunability of surface properties like stiffness and wettability, surface functionalization with bioactive molecules or designing 3D patterns at micro or Nano scales are widely exploited strategies used for triggering specific cell response for development of smart polymers for tissue engineering applications like cell sheet engineering, smart biomineralization heart valves and vascular graft tissue engineering, drug delivery, cell recruitment and development of highly smart and efficient medical devices for diagnosis and therapeutic treatment of various diseases [10-12]. Moreover, they are also used as polymer binders in development of more efficient rechargeable batteries for electrification of grid and automotive transportation by providing mechanical stability of the electrode [13].

II. TYPES OF SMART POLYMERS

Smart polymers, scientifically referred to as stimuli-responsive polymers, are a distinct category of materials that exhibit exceptional characteristics and experience reversible alterations in their physical or chemical properties when exposed to particular external stimuli. These polymers can be categorized extensively according to their sensitivity to specific external stimuli namely temperature sensitive, pH sensitive, photosensitive, enzyme responsive polymers and inflammation responsive polymeric systems [14].

1. **pH Sensitive:** These polymers show sensitivity towards variation in pH of the surrounding environment. These polymers exhibit swelling or collapse transitions as a result of the process of protonation or deprotonation of functional groups. This phenomenon allows for utilization of sensing applications in biological systems or to controlled release of drugs. They include weak polyacid components for example poly (acrylic acid) and Poly basic moieties for example Poly (N-diethylaminomethyl methacrylate) etc. In their structure which protonate and deprotonated the molecule depending on the pH of surrounding. These polymers are extensively used in personal care products, biomedical fields, water remediation and other industrial processes [15].

2. **Photosensitive Polymers:** Light-responsive polymers, scientifically referred to as photo responsive polymers, demonstrate alterations in their characteristics when subjected to light of particular wavelengths. Conformational changes, crosslinking, and degradation are potential phenomena that these entities can experience, presenting opportunities for utilization in various fields including optical devices, drug delivery systems, and microfabrication processes. They find importance in various applications like functional

micro patterns, drug delivery systems, photodegradable materials, photo-switchable liquid crystalline elastomers for remote actuation, etc. [16].

3. **Enzyme-Responsive Polymers:** These polymers respond to selective enzymes and serve as a major connecting link between artificial materials and biological entities by integrating the polymeric properties with specific biological processes. They also show reversible and visual responses to enzymes in formulations like cell support, injectable scaffolds drug delivery systems, etc. [17].

4. **Inflammation-Responsive Polymeric Systems:** These polymers show responsive behavior towards the certain changes in the ambiance which in turn are the result of inflammatory responses of the body, including augmented permeability of blood vessels, upregulation of definite cell surface receptors, reduced pH, high oxidative stress, etc. these polymers find immense application in the medical community. [18]

5. **Temperature Sensitive Polymers:** Polymer which shows transitional behavior from monophasic to biphasic as a function of varying temperature are termed as temperature sensitive or temperature responsive polymers that retort to temperature variations especially those that undertake phase transition in aqueous medium have attractive distinct attention due to their potential application in biomaterial field, architecture and water recovery strategies. These materials have the ability to experience reversible phase transitions, such as sol-gel transitions or alterations in swelling behavior, which renders them well-suited for various applications such as tissue engineering and drug delivery [19,20].

Temperature variations can be induced externally in an invasive manner and natural occurrence of spontaneous temperature fluctuations during day-night cycles. This feature has inclined the interest of the scientific community towards extending the research parameters towards the field of temperature-sensitive smart polymers. Based on various working mechanisms, temperature sensitive polymers can be classified into three major classes, namely [21].

- **Shape Memory Polymers:** shape memory polymers (SMPs) regain their original or permanent shape either after a deformation upon exposure to external stimuli i.e., by changing the temperature of the environment. They demonstrate programmable shape memory effect (SME). SMPs are thermoplastic elastomers having a hard phase and high glass transition temperature, i.e., T_p and T_{g1}, and a second switching phase with intermediate T_{g2} or melting temperature that imparts the temperature response behavior to these polymers. On subsequent deformations between more than one transition temperature, a temporary shape forms, which can be frozen by cooling. The Thermal responsive behavior of this cycle is tunable by changes in cycles. The invasion of multiple intermediate temperature transitions leads to an increase in the programmable shape changes. For example, it is found that it is possible to induce four independent states into a shape memory material having one broad glass transition temperature [22,23].

- **Liquid Crystalline Polymers:** These polymers contain an additional anisotropic liquid crystalline phase (LCP) Besides the glassy and rubbery isotropic phase, these polymers having main chain nematic liquid crystalline blocks have an elongated main chain in LCP, which condenses to a coiled state by providing higher temperature to rubbery phase i.e., fully reversible polymers phase transition. This feature has been used in a switching mechanism in the processing of artificial muscles. Polymer networks with side chain mesogens with chiral liquid crystalline polymer networks have been used in LCD screens and also in the development of thermochromic materials [24].

- **Thermo-Responsive Polymer Solutions:** These polymers undergo liquid-liquid phase transition when exposed to the environment with variation of temperature in these polymers concentrated polymer phase and a diluted polymer phase gets separated from the homogeneous solution phase. This transition can be observed visually by observing the transparency of the solution i.e., the clear solution gets converted to a cloudy solution, and the corresponding phase transition temperature is termed as cloud point temperature (T_{CP}) which is result of the formation of nano droplets of higher concentration polymeric solution in the polymer solution of low concentration having different refractive indexes [25].

  When heat is provided for separation of the phases then this type of transitions is termed as the lower critical solution temperature. Whereas when phase separation occurs upon cooling then this is termed as upper critical solution temperature. Initially LCST behavior was observed in Poly (methyl methacrylate) PMMA observed in an organic solvent of polymer behavior of polymer polystyrene was observed in organic solvents, two propanone and cyclohexane respectively.[26]

III. PRINCIPLES OF TEMPERATURE RESPONSIVE POLYMERS IN AQUEOUS SOLUTION

An aqueous solution of homopolymers exhibit different type of polymer phase transition namely

- Lower critical solution temperature (LCST) transition
- Upper critical solution temperature (UCST) transition
- Close loop coexistence transition

In LCST transitions, concentration of the second phase of polymer increases with increase in temperature above LCST whereas in UCST polymers concentration of second phase increases at equilibrium with decrease in temperature till UCST [27]. In closed loop coexistence phase transition, the second phase lies between the temperature difference range of LCST and UCST shows in figure 1. It is reported for few polymers which coincide with LCSD and UCST phase behavior, for example in poly (ethylene glycol) (PEG) in which both LCST and UCST transitions can happen when heated at the temperature greater than the boiling point of water i.e., 100 ^{O}C/min in closed vessels. Moreover, partially acetylated Poly (vinyl alcohols) and Poly (hydroxyethyl methacrylate) also exhibit close-loop coexistence behavior [28,29].

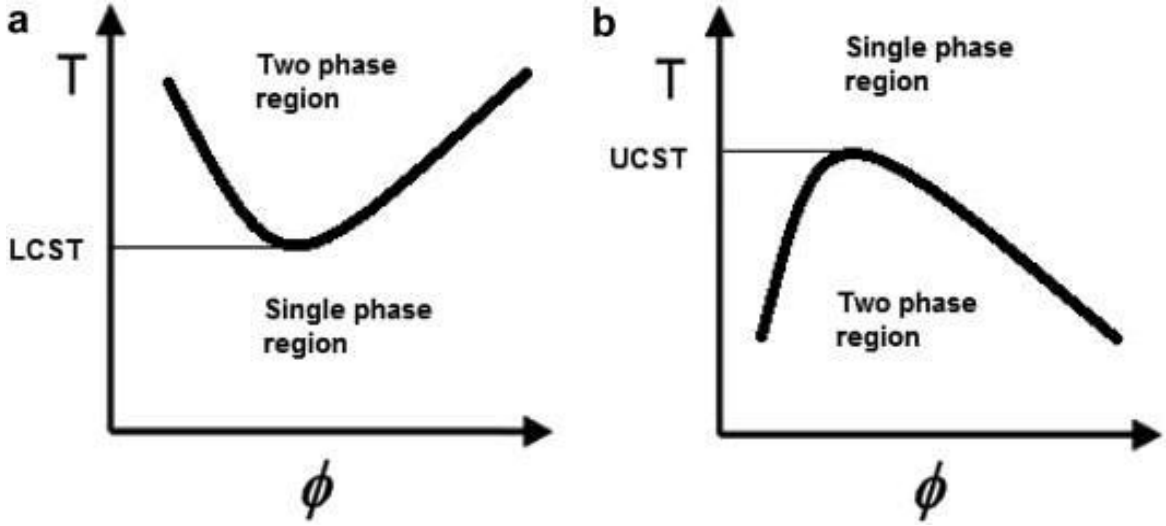


Figure 1: Schematic illustration of phase diagrams for polymer solution (a) lower critical solution temperature (LCST) behavior and (b) upper critical solution temperature (UCST) behavior.

The phase transition temperature of thermos-responsive polymers is determined by assessing the turbidity using a light scattering technique within the wavelength range of 500-700 nm while varying the temperature. This evaluation is conducted at a specific concentration of the polymer [30]. In order to mitigate experimental uncertainties and facilitate the comparison of T_{cp} values obtained from various experimental configurations and instruments, the turbidity method is employed. This involves measuring T_{cp} by utilizing a 10mg/ml concentration and subjecting the sample to controlled heating and cooling rates of 0.5°C per minute. The readings are obtained at a scattering wavelength of 600 nm, which ensures the acquisition of reliable and resilient data [31, 32].

IV. MECHANISM OF LCST AND UCST POLYMER PHASE TRANSITION IN AQUEOUS SOLUTION

1. **Polymers with LCST Behavior:** Polymers exhibiting a Lower Critical Solution Temperature (LCST) phase transition in an aqueous environment demonstrate solubility in water at comparatively lower temperatures, while phase separation occurs at higher temperatures [33]. This observation indicates that the Gibbs free energy associated with the dissolution of the polymer in a solvent, specifically water, becomes negative at lower temperatures and transitions towards a positive value as the temperature increases. Therefore, the enthalpy of dissolution (ΔH) exhibits a negative value, thereby facilitating the formation of hydrogen bonds between water molecules and polymer chains [34]. This phenomenon, in turn, promotes the hydration of polymer chains. The negative entropy contribution suggests that the process of hydrating polymer chains leads to a decrease in the entropy of water molecules [35]. When the temperature is raised, the strength of hydrogen bonding between polymeric chains and water molecules decreases. As a result, the entropic term, represented by T ΔS, increases. This increase in entropy contributes to a positive value of Gibbs free energy, which ultimately causes the phases to separate. It can be postulated that elevated temperatures induce partial dehydration of the polymer

chain, resulting in the collapse and subsequent aggregation of the polymeric phase [36]. It is important to observe that there is partial dehydration of polymer chains during the phase transition known as the LCST. It should be noted that complete dehydration of polymeric chains does not occur during this phase transition. Additionally, the extent of polymer dehydration is dependent on its hydrophilic properties. As the hydrophilic nature of the polymer intensifies, the degree of dehydration of the polymeric chain diminishes, and conversely. In theory, it can be postulated that every water-soluble polymer should demonstrate a LCST phase transition when placed in an aqueous environment. However, experimental observations have shown that this phase transition is not always observed, particularly in water under normal atmospheric pressure. In certain cases, such as with PEG, extended heating at higher temperatures may be necessary to induce the phase transition. Therefore, the transition temperature of a polymer, known as T_{CP} or LCST, is influenced by its molecular structure. It is possible that polymers with higher levels of hydration may have higher LCST values compared to polymers with lower levels of hydration. Moreover, the augmentation of the molecular weight of the polymer enhances the polymer-polymer interaction, consequently causing a decrease in the polymer's hydration efficiency. This ultimately leads to a reduction in the LCST [37, 38, 39].

2. **Polymers with UCST Behavior:** The UCST polymer exhibits analogous characteristics to LCST polymers in terms of hydration upon dissolution, resulting in negative changes in enthalpy (ΔH) and entropy (ΔS) for hydration. The LCST (Lower Critical Solution Temperature) transitions are characterized by cooperative entropy-driven processes, while the UCST (Upper Critical Solution Temperature) transition is associated with an enthalpic process. The transition temperature in UCST (Upper Critical Solution Temperature) material exhibits a direct correlation with the intensity of the supramolecular interactions. This is because the phase transition of UCST in water primarily relies on associative interactions. These associative interactions get lost by polymer dissolution. If the released energy is greater than the energy gained by dissolution, then it can resist the solubility behavior of the polymer. However, the strength of supramolecular associative interactions decreases with a rise in temperature thus increasing the value of hydration term which leads to dissolution of polymer. However, the hydrophilicity of the polymer should be prominent enough to render its LCST transition (lowered than UCST transition) that leads to complete insolubility. This suggests that transition temperature increases by the introduction of hydrophobic side chains in polymer structure and the effect is known as the Counterintuitive effect. Including hydrophobic side chains in the polymer leads to a decrease in its solubility and a reduction in the LCST transition. However, these side chains also generate a hydrophobic atmosphere that promotes associative interactions through hydrogen bonding. As a result, the UCST the transition temperature is increased [40-41].

V. MAJOR TEMPERATURE-RESPONSIVE POLYMERS IN AQUEOUS SOLUTION

Both LCST and UCST polymers exhibit thermo-responsive behavior in an aqueous medium in general, LCST behavior is shown by water-soluble polymers, but not all polymers show LCST behavior in an aqueous medium at unit atmospheric pressure and between 0 -100 °C for which hydrophilic moieties like amide and ethers and hydrophobic moieties life short aliphatic groups are introduced in a balanced ratio [42].

For the simplified study the thermos-responsive polymers are classified in two categories;

1. **LCST Polymers:** LCST phase transition is exhibited by copolymers on heating having balanced hydrophilic and hydrophobic nature polymers having both simpler structure like poly (propylene oxide-co-poly (ethylene oxide) copolymer and complex polypeptide with repetitive unit Val-Pro-Gly-Val-Gly (VPGVG) shows LCST behavior. This section will provide an elaborated account on most vividly explored five major classes of LCST polymers, namely

   - **Poly(acrylamide)s and Poly (vinyl amides):** Polyacrylamide includes temperature responsive behavior of PNIPAm and PVCL and their analogous like Poly (N-cyclopropyl acrylamide), Poly (N, N-diethyl acrylamide), Poly (N-vinyl piperidine) and several other for substituted Poly(N-vinylpyrrolidone) etc. Poly (N-isopropylacryl amide) (PNIPAm) was the first reported thermoresponsive polymer in aqueous solution. LCST of PNIPAm lies between body and room temperature means around 30°C and suggests its robust phase behavior and potential to be used for biomedical applications. LCST of PNIPAm shows almost non dependency on chain length with regards to polymer concentration. means minor variation in solution pH and polymer concentration do not induce prominent change in T_{cp} or LCST [43,44]

     After PNIPAm, poly (N-vinyl caprolactam) (PVCL) was coming into consideration having LCST at 31 °C but PVCL and PNIPAm showed biocompatible nature which qualifies them as ideal candidates for biomedical applications. it was found that both of the above-mentioned polymers share common drawback of having very high glass transition temperature (T_g) due to which vitrification of highly concentrated polymers takes place throughout phase separation which induces hysteresis amongst heating and cooling transitions [45]

     The monomers PNIPAm and N-vinyl caprolactam (VCL) were polymerized via a free radical method using azobis isobutyronitrile as a common radical initiator in a controlled radical polymerization process. The implementation of Controlled radical polymerisation CRP for both monomers results in the acquisition of well-defined polymeric characteristics, such as precise chain length, narrow distribution of molecular weights, and clearly defined end groups. These particular attributes are essential for materials utilized in biomedical applications. The controlled terminal groups exhibit a preference for direct modification and conjugation with biological entities [46].

     The radical polymerization mechanism of VCL and NIPAM allows for the synthesis of a diverse range of copolymers using readily accessible vinyl monomers. By incorporating inert comonomers with varying hydrophilicity, it becomes possible to adjust the T_{cp} of the resulting copolymers. This tunability of T_{cp} introduces a means to control the temperature-responsive behavior of these polymers. In addition to this, the Co-monomers have the ability to be interchanged in accordance with various stimuli, resulting in the creation of copolymers that are responsive to multiple stimuli. For instance, by introducing pH-switchable side chains, the copolymers become responsive to changes in pH. Similarly, by incorporating UV switchable side groups

like azobenzene or spiropyran moieties, the copolymers become responsive to UV light. This information is supported by reference [47].

- **Poly (oligo ethylene glycol [meth]acrylates):** High glass transition temperature, formation of hysteresis, cumbersome since synthesis of NIPAM by CRR suggested the need of research on alternative LCST polymers which gives rise to inclination of research interest towards another polymer i.e., poly(oligo ethylene glycol[meth] acrylates)s (POEGMA)s constituted by Poly (meth)acrylate backbone incorporated with oligo ethylene glycol side chain. T_{cp} of POEGMAs prepared from living anionic polymerization methods exhibit tunability by systematically varying the functionality of oligo ethylene glycol chains and also by varying the number of repetitions of ethylene glycol units. It was observed that both POEGMAs and PNIPAm exhibit similar thermos-responsive behavior with respect to molecular weight and concentration dependence of T_{cp} straightforward CRP, commercial availability and lower glass transition temperature of POEGMAs makes it a more desirable material over PNIPAm. POEGMAs are prepared by free radical polymerization as that of poly(acrylamide)s and poly (vinyl amides)s. CRP and anionic polymerization methods result in defined end groups and polymer structure. Furthermore, tunability of POEGMAs, thermo responsive behavior can be extended by copolymerization other (meth)acrylate co monomers which in turn regulates the hydrophilicity/ hydrophobicity of polymer resulted in tuned T_{cp}. Moreover, POEGMAs also showed multiple response behaviors as that of PNIPAm and PVCL by incorporation of multi responsive comonomers sensitive to stimuli such as pH or UV radiation [48].

- **Poly (methyl vinyl ethers) (PMVE):** PMVE demonstrates an LCST phenomenon characterized by a Tcp of 34 °C. The phase diagram of PMVE exhibits two discernible peaks, with one peak influenced by the molar mass of the polymer, akin to PVCL. The second peak, which is observed at elevated polymer concentrations, exhibits no correlation with the molar mass of the polymer and bears resemblance to PNIPAm. In addition to PMVE, several poly (vinyl ethers) modified with ethylene glycol have also exhibited thermos-responsive characteristics. The Tcp of these polymers can be modulated by manipulating the end group and chain length of the ethylene glycol polymers. A slow polymerization process and the formation of polymers with low degrees of polymerization characterize the free radical polymerization of vinyl ether. Poly (vinyl ether) is commonly synthesized through the utilization of living cationic propagating species that incorporate ether groups. The cationic polymerization process entails the establishment of an equilibrium state between cationic propagating entities and dormant covalent entities. The establishment of this equilibrium enables the progression of cationic polymerization of vinyl ethers, leading to the creation of polymers with accurately determined terminal groups. The provided dataset comprises three numerical values [49,50].

- **Poly (2-oxazoline):** These are synthetic polyamides that consist of a tertiary amide group in the repeating unit and a variable side chain, such as a methyl side chain, which gives them a strong hydrophilic nature. They do not exhibit a LCST phase transition in water. However, when the length of the hydrophobic side chain is increased to ethyl or propyl, they exhibit thermo-responsive LCST behavior. An empirical observation was made that the T_{cp} of a polymer decreases as the length of

the chain is extended. For instance, the T_{cp} of Poly (2-ethyl-2-oxazoline) is approximately 60 °C, whereas polymers with side chains consisting of n-propyl groups, such as nPropOx, exhibit a T_{cp} of around 25°C. There exist multiple copolymers (2-oxazoline) that possess diverse side chains, which are obtained through Co-polymerization or post-polymerization modifications, allowing for accurate adjustment of T_{CP}. The polymerization of 2-oxazoline monomers can be initiated by electrophilic initiators such as methyl tosylate or methyl triflate. This process involves the opening of a living cationic ring, leading to the formation of Poly (2-oxazoline). During the preparation process, the monomers attack the initiator, resulting in the formation of a cationic oxazolium species. Subsequent attacks by additional monomers cause ring opening, and the added monomers become cationic oxazolinium chain ends. As a result, this process yields well-defined polymers with controlled chain end functionalities [48,51].

- **Polyphosphoric Esters:** Polyphosphoric esters represent a freshly identified category of polymers that exhibit biocompatibility and biodegradable properties These polymers consist of a main chain composed of hydrolyzable phosphoester groups. Thermo-responsive poly(phosphoester) is synthesized via the equilibrium between hydrophilic phosphoester groups and hydrophobic alkoxy side chains, specifically ethyl oxy or isopropoxy. These polymers exhibit an LCST of 38 °C and 25 °C, respectively. Poly(phosphoester)s are synthesized through the process of ring-opening polymerization of cyclic 2-alkoxy-2-Oxo-1,3,2-dioxaphospholane using a catalyst and alcohol as an initiator. In order to produce well-defined and metal-free poly(phosphoester)s, the catalyst is replaced with organic bases such as 1,8-diazabicyclo [5,4,0] undec-7-ene (DBU) or 1,5,7-triazabicyclo [4,4,0] dec-5-ene (TBD) [52].

2. **UCST Polymers:** Few thermoresponsive polymers in water exhibit UCST behavior under normal pressure conditions. This behavior arises from strong supramolecular interactions between polymer chains, such as hydrogen bonding and electrostatic forces of attraction. The UCST phenomenon observed in polymers dissolved in aqueous solvents can be attributed to the attractive hydrogen bonding interactions between the primary amide groups found in the polymer side chains. This interaction induces the UCST behavior, particularly in the absence of ionic impurities, which can occur due to partial hydrolysis of the side chains. Poly(betaine)s are widely recognized as the predominant class of polymers that demonstrate UCST behavior when dissolved in water. These polymers are characterized by their zwitterionic nature, wherein each repeating unit contains both positive and negative charges. Poly (2-dimethyl [methacryloxyethyl] ammonia propane sulfonate) (PDMAPS-MA) and Poly (3-[N-(3-propyl)-N, N-dimethyl go profile N dimethyl] ammonium propane sulfonate) (PDMAPS - MAM) are widely recognized as the most prevalent poly(betaine) compounds exhibiting UCST behavior. The phase behavior of PDMAPS-MA exhibits a significant dependence on the length of the polymer chain. The attainment of UCST phenomenon in water can be accomplished through the interplay of polyelectrolytes and multivalent counterions, leading to the manifestation of UCST behavior in the polymer-water system. Additionally, the alcohol-water solution is comprised of a hydrophobic polymer that possesses hydrogen bond-accepting functional groups, such as esters, ethers, tertiary amides, and so on. Polymers that exhibit UCST behavior in solvent interactions have been observed in ethanol-water

systems. This behavior can be achieved by incorporating photo-switchable or redox switchable units into polymers such as poly (methyl [meth]acrylate)s, poly(2-oxazoline)s, and POEGMAs. These polymers are examples of thermoresponsive polymers that demonstrate UCST behavior when exposed to a mixture of alcohol and water as the solvent [53-56].

VI. APPLICATIONS OF THERMAL RESPONSIVE POLYMERS

1. **Delivery of Therapeutic Molecules - Drug Delivery:** Drug delivery is a process for the administration of bioactive therapeutic compounds (drugs) in the human/animal body at the right site, in the right concentration, and at the right rate. But the complexity of the designing and working of the human or animal body creates several barriers for efficient drug delivery including low solubility of drugs, enzymatic degradation, fast clearance rates from body, inability to cross the biological barriers, nonspecific & toxicity etc. For efficient and desired drug delivery polymers are used as the carrier of the drugs. The desired controlled drug delivery is a characteristic of zero order kinetic rate which is not easily achievable. For the purpose of efficient drug delivery smart polymers come into play due to their ability to deliver the drug molecules at the right time and concentration at specific sites in response to external stimuli illustrating in figure 2. For example, in response to elevated temperatures the polymer chains of drug carriers can expand resulting in drug diffusion at the specific site and concentration. [34-36,57]

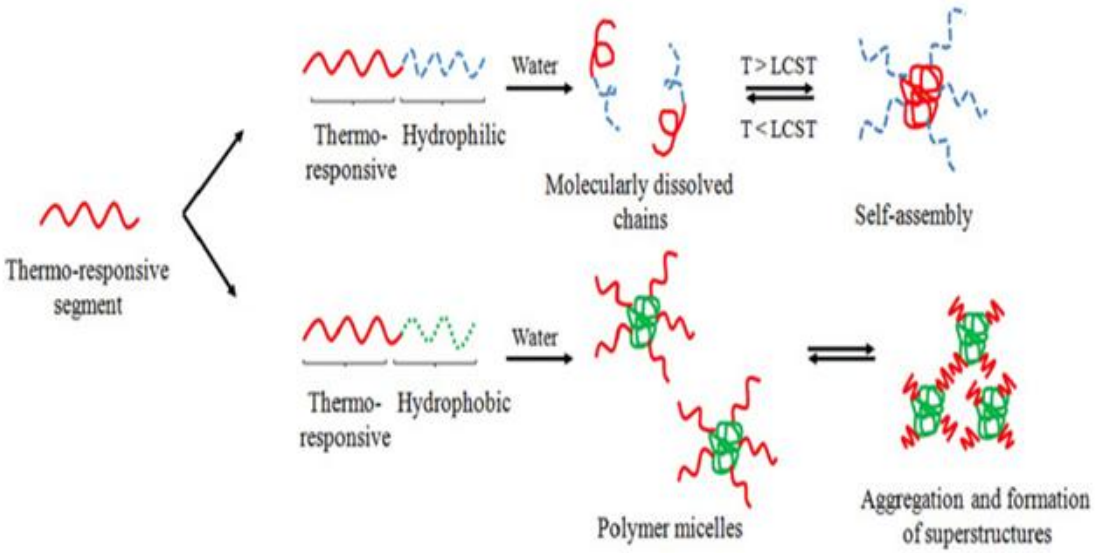


Figure 2: schematic illustration of drug delivery mechanism of thermally responsive polymers.

2. **Gene Delivery Transfection:** Gene delivery is a specialized methodology specifically developed for the therapeutic intervention of genetic disorders through the rectification of malfunctioning genes. The technique of correcting defective genes involves the introduction of therapeutic gene DNA into cells, which subsequently replaces, repairs, and regulates the malfunctioning genes. However, the transportation of DNA to the cell nucleus poses a significant challenge due to the DNA molecule's negative charge and

hydrophilic nature. To successfully deliver DNA to the nucleus, it must traverse the negatively charged and hydrophobic cell membrane shows in figure 3. To address this issue and achieve delayed delivery of DNA to the nucleus, smart materials have been identified as a suitable choice of materials and cleaning methods. Smart materials have been widely used as preferred materials for delivering DNA to the nucleus. Gene delivery using cationic polymers involves three primary stages: DNA complexation, carrier traversal through the cell membrane and cytoplasm, and DNA release into the cytoplasm and subsequently the nucleus. Typically, complexation occurs at ambient temperature, while incubation and transfection periods are conducted at 57 °C. Thermo-responsive polymers undergo temperature variations during the processes of complexation, incubation, or transfection, resulting in an improved transfection efficiency for gene therapy. In a scientific investigation involving the utilization of thermos-responsive polymers such as polyethyleneimine (PEI) with grafted PNIPAAm, chitosan grafted with PNIPAAm, linear and branched NIPAAm, DMAEMA and PEI polymers, and PEG polymers with grafted PEI, the transfection efficiency was improved by modifying the complexation and transfection temperatures [57-59].

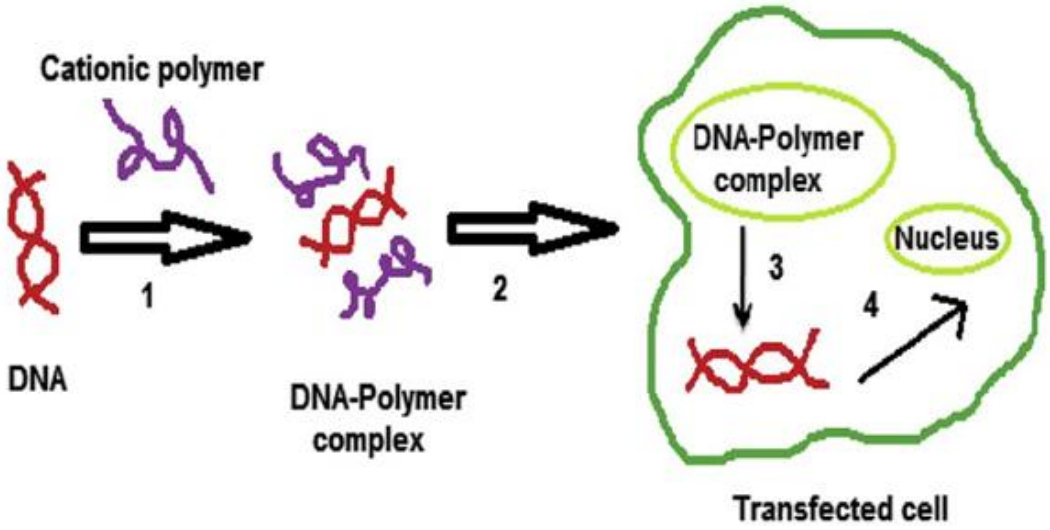


Figure 3: Gene delivery transfection by thermally responsive polymers.

3. **Cell Detachment from PNIPAm Surfaces:** Cell culture is the primary requirement of all the biomedical research including cultivation of cells, tissue and organoids like constructs for regenerative medicine and Cancer Research. Cells are adhered, grown and differentiated into desired tissue by Seeding onto tissue culture surfaces. Thermo-responsive polymers Specifically, LCST polymers provide the surface for harvest of unharmed and interconnected monolayers. Change in confirmation and hydration state of the substrate enables the detachment of the cells. For example, in PNIPAm polymers cells are seeded and cultivated above the LCST (≃37 °C), which results in increasing the ratio of globular confirmation of PNIPAm and exposing the hydrophobic isopropyl groups. In 1982 Grinnell et al showed that binding between ECM and cells is also active below the LCST i.e., 4 °C, which indicates that weakening of ECM substrate interaction is the driving force behind the cell detachment process. Fibronectin and Laminin are examples

of ECM proteins with these improvements which show weak interactions with the surface due to hydrogen forces and initiates the Cell detachment process. In a study, it was found that active ATP consuming recognition of cytoskeleton and signal transduction are prerequisites for complete cell detachment represented in figure 4. Acting based stress fibers of adhering cells establish an equilibrium between pulling force of cytoskeleton and tensile strength by exerting traction and contraction forces. However, depression in temperature weakens the surface binding of ECM with attachment and rounding of cells due to prominent attracting force of metabolically active cells as compared to stress of ECM. Similarly, Cell detachment also takes place in cell sheets but rolling and contraction due to strong cell-cell junction leads to recovery of cell sheets. Detachment process on a thermoresponsive substrate is dependent on the type of cell, ambient temperature, type of proteins adsorbed and several other surface properties. [57-58, 60-61]

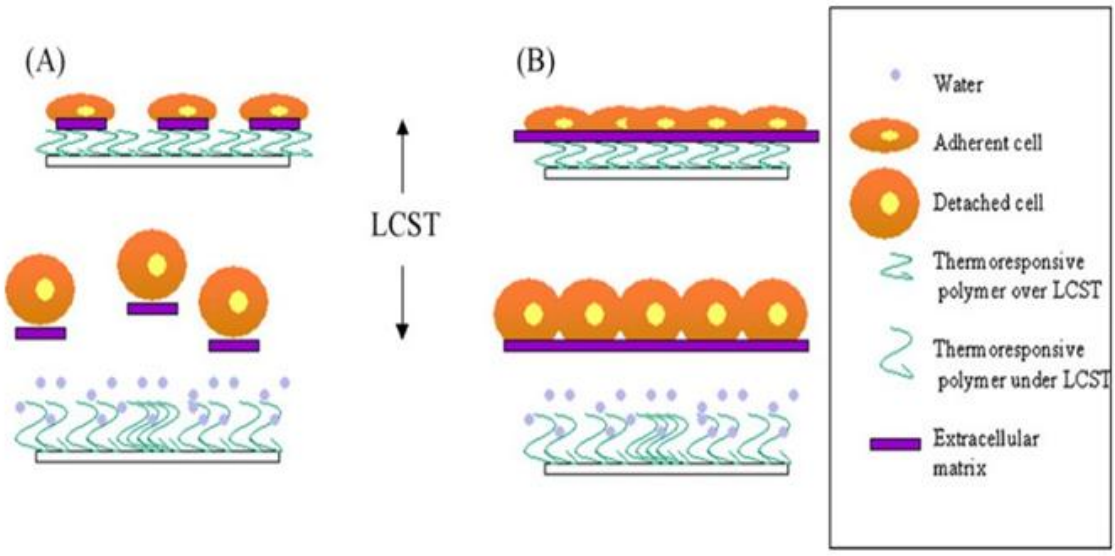


Figure 4: Cell Detachment Mechanism of PNIPAm.

4. **Cell Tissue Engineering:** PNIPAm is a thermos-responsive polymer used in successful detachment of cell monolayer in cell culture with advancement in research parameters; some cell sheets have achieved clinical approval and are extensively used as substrates. Cell sheets are used in regeneration, and replacement of several nonfunctioning and damaged tissue. Cell sheet engineering is a sequence of processes including fabrication of homotypic, heterotypic, monolayer or multilayer sheets of cell on substrate grafted with thermos-responsive polymers represented in figure 5.

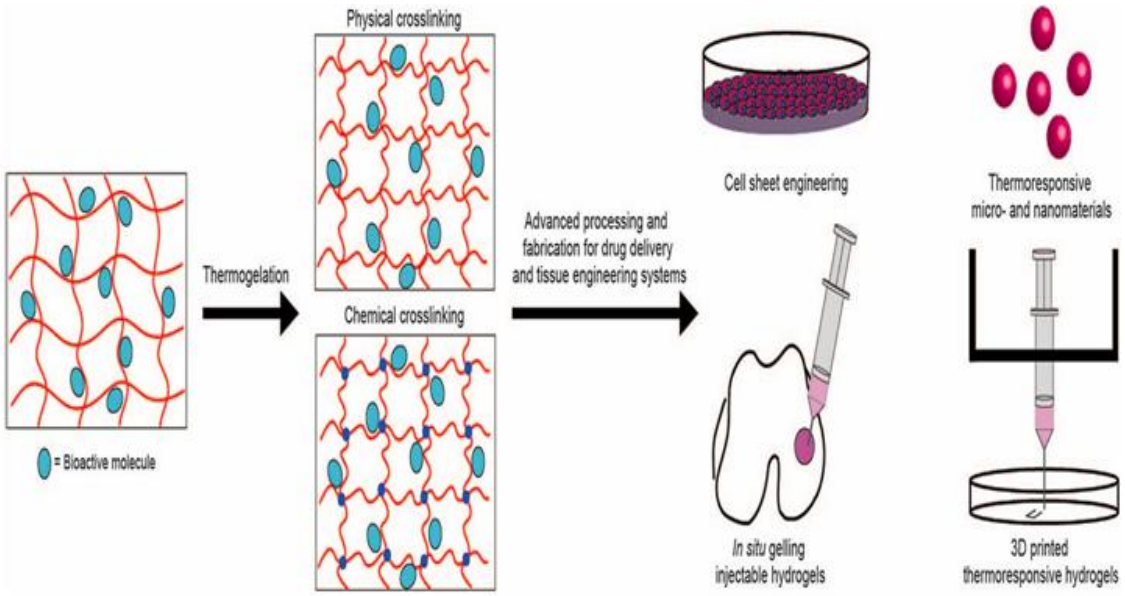


Figure 5: schematic representation of tissue engineering mechanism.

Corneal epithelial reconstruction is one of the most prominent examples in which a single cell sheet is used. When the cornea of the eye is damaged, biopsy is performed for availing autologous corneal stem cells for generation of confluent monolayers of cell for treatment as a replacement of damaged cornea. Also, in the absence of corneal stem cells as in case of cornea failure autologous epithelial cells can be taken from oral mucosa epithelium. Cell sheet engineering is clinically applied and available for regeneration of esophagus and after endoscopic submucosal dissection in which temperature-based detachment of cultivated autologous cell sheet takes place for transplantation on the outer surface of esophagus. This is how CSE can provide an alternative method for surgical treatment of esophagus. the Multilayered cell sheets are also used for regeneration of periodontal and cartilage tissue. In this case monolayer sheets are fabricated from the periodontal ligament which are stacked in two to three layered constructs after temperature sensitive cell detachment. Similarly, regeneration of cartilage tissue is also carried out by culturing the chondrocyte sheets and stacking them to form multilayered sheet construct which can be transplanted on the place of cartilage defect. Also, this cell sheet technology for tissue engineering and regenerative therapies are used for treatment of air leaks in lungs by fabrication and transplantation of tissue engineering construct fabricated from dermal fibroblast cells sheets.

In addition to the aforementioned keratinocyte cell sheets, pancreatic islet cells and mesenchymal stem cells have also been artificially produced and effectively utilized in the treatment of patients. Hepatocytes and endothelial cell sheets (heterotypic) are utilized in the production of liver tissue through TE techniques. This is due to the synergistic effect of combining these cell types, resulting in the development of hepatocytes tissue that exhibits normal functionality. However, the restricted oxygen delivery to the central area of the tissue engineering construct poses a constraint on the extensive development of transplants at a macroscopic level. Likewise, when it comes to tissue engineering constructs designed for thick cardiac tissue, the cells experience

necrosis as a result of inadequate oxygen and nutrient delivery. It is important to acknowledge that all of the aforementioned cell sheets are fabricated using PNIPAm graft cell tissue culture. In order to create intricate organs such as kidneys and livers, a variety of cell types are required for the fabrication of heterotopic tissue, patterned thermos-responsive surfaces, and other necessary components. In a study, heterotypic tissue was created using a three-step procedure involving the copolymerization of PNIPAm and n-butyl methacrylate (BMA) side chains, each with distinct transition temperatures. Hepatocytes, when placed at a temperature of 37°C, are observed to adhere to the co-culture with endothelial cells, which are located on the PNIPAm-co-BMA region at a temperature of 27°C. In a separate investigation, it was discovered that surfaces modified with PNIPAm through copolymerization alongside diethyl glycol methacrylate (DEGMA) could be fabricated through the utilization of low-pressure plasma treatment. Surfaces that have been prepared demonstrate transitions arising at temperatures slightly higher than those found within the physiological range. The study unveiled that human corneal epithelial cells (HCEC) exhibit adhesion, spreading, and proliferation on these surfaces. The copolymer surface demonstrated superior performance compared to conventional PNIPAm surfaces, primarily due to its more effective and less aggressive cell harvesting procedure. The range of values is between [62-65]

5. **Miscellaneous – Thermos-Responsive Polymers as Nanocarriers for Biomedical Applications:** The latest studies and progress in the field of nanoscience and technology have brought forth the concept of nanomedicine as a highly promising strategy for addressing the issues and obstacles related to drug delivery. Additionally, nanomedicine has the potential to enhance the effectiveness of active pharmaceutical ingredients (API) by modifying their pharmacokinetics (how drugs move within the body) and biodistribution (how drugs are distributed throughout the body). Polymer nanocarriers effectively encapsulate drugs, providing protection to delicate molecules against premature degradation and metabolization. Additionally, they enhance the solubility of sparingly soluble or insoluble drugs and contribute to an improved plasmatic half-life. In addition to their ability to act as nanocarriers, these nanoparticles also exhibit favorable tumor penetration capabilities, making them highly promising for diagnostic purposes. Specifically, they enable targeted imaging of diseased tissue and facilitate the monitoring of disease progression. The nanocarriers exhibit a wide variety of configurations, encompassing albumin-based compositions, nanoparticles incorporating metals, liposomes, micelles, and polymeric nanoparticles. Stimulus-sensitive nanoscale systems are preferred over alternative nanocarriers due to their ability to provide efficient and precise treatment by enabling site-specific drug delivery. Among various stimuli, temperature is considered to be one of the most favored options, as tissues have the ability to endure moderate hyperthermia up to 43°C for an extended duration, resulting in reversible outcomes. The mild hyperthermia can be induced by various sources such as microwaves, ultrasound, radio frequency, infrared illumination, and magnetic field. The responsiveness of nanocarriers to stimuli enables the development of less invasive treatment approaches compared to conventional surgical procedures. In the present scientific landscape, a significant amount of effort has been dedicated to exploring the utilization of thermos-responsive polymers in the field of medicine, specifically examining their impact on cellular behavior in controlled laboratory environments (in vitro) or within living organisms (in vivo) using animal models [66-67].

VII. CONCLUSION

Thermo-responsive polymer specially those exhibiting temperature induced phase transition i.e., LCST and UCST polymers have inclined the interest of the scientific community for further research and development in this field. LCST polymers have been reported majorly due to their ability of phase transition in aqueous medium (water soluble). Besides this the gold standards of LCST polymers i.e., PNIPAM has lost terrains to alternatives like POEG(M) AND poly(2-oxazoline) with tunable Tcp and reduced hysteresis between heating and cooling cycles. Unlike LCST, UCST polymers do not have the wide variety of polymers undergoing UCST transitions in aqueous medium due to their high sensitivity towards minor impurities and ionic strength of solution. This suggests the need for development of polymers exhibiting robust UCST transition in aqueous solution. Furthermore, thermos-responsive polymers are widely explored for applications in biomedical usage in various forms including drug carriers for site specific and efficient drug delivery, delivery agents of DNA for successful gene therapy, substrate for developing implants for tissue engineering etc. Moreover, recently they are also discovered as potent nanocarriers for nanomedicine.

VIII. RESEARCH AND FUTURE SCOPE

Multidisciplinary research has been performed in the past decades to make advances in thermos-responsive smart polymers and their applications. Progress in compositional advances in new temperature responsive polymers is expanding the ability to prepare macromolecules with topological complexity so that comparatively less popular and unexplored polymers can be utilized for greater roles in future. Moreover, for consistent development in composition of temperature responsive polymers more work is needed to be devoted by the interdisciplinary branches including organic chemist, polymer chemist, physicist, biologist, material engineers, pharmacist, and medical practitioners for fulfilling the needs of modern world that in turn will improve the quality of life.

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