Life Science Informatics Publications

Research Journal of Life Sciences, Bioinformatics, Pharmaceutical and Chemical Sciences

Journal Home page http://www.rjlbpcs.com/

RJLBPCS

ISSN 2454-6348

Original Review Article **DOI: 10.26479/2024.1005.03**

ROLE OF THERMORESPONSIVE MICROGELS IN RECENT ADVANCEMENT OF DRUG DELIVERY VEHICLES: A REVIEW

Javed Akhtar[1], Anmol Kumar[1], Shubhangi Pandey[1], Krishna Kumar[2], Shikhi Sahai[1], Kranthikumar Tungala[1]*

1. Department of Chemistry, Ewing Christian College, University of Allahabad, Prayagraj, Uttar Pradesh-211003, India.
2. Department of Chemistry & Environmental Science, Madan Mohan Malaviya University of Technology, Gorakhpur, Uttar Pradesh-273010, India.

ABSTRACT: The size of microgels ranges from 10 nm to 100 µm making them small intra-molecular crosslinked macromolecules that have been exploited as carriers for drug delivery with targeted delivery at a specific part of the body. Fabrication of stimuli responsive drug delivery systems for a drug provides a chance for increased patient compliance, better safety profile and efficacy. In recent times, biocompatible polymer based carriers are investigated widely and have found applications as controlled and sustainable release systems in pharmaceutical industry. Microgels can encapsulate drugs and respond to environmental cues such as pH, temperature, or ionic strength. When triggered, they release the drug payload precisely where needed, minimizing side effects. Controlled release applications have seen extensive studies of microgels made from thermally responsive polymers. In addition to drug delivery, poly-(N-isopropylacrylamide) (PNIPAM) based microgels possess special responsiveness and combine both nanoparticle and hydrogel benefits thus become very useful in various biomedical areas. We therefore aim at highlighting some recent advancements in the development of drug delivery vehicles based on thermoresponsive PNIPAM microgels.

Keywords: Thermoresponsive microgel, biocompatible, drug delivery, stimuli-responsive.

Article History: Received: Sept 18, 2024; Revised: Sept 24, 2024; Accepted: Sept 27, 2024.

Corresponding Author: Dr. Kranthikumar Tungala, Ph.D.
Department of Chemistry, Ewing Christian College, University of Allahabad, Prayagraj, Uttar Pradesh-211003, INDIA. Email Address: drkktungala@gmail.com

1. INTRODUCTION

A variety of biomedical applications have demonstrated the usefulness of hydrogels, a type of biomaterial that consists of three-dimensional polymeric networks that can absorb substantial volumes of water or biological fluids. Hydrogels are a promising class of materials for tissue engineering, pharmaceutical applications, and biomaterials science due to their swelling property as well as their biocompatibility, good mechanical properties, tunable chemical structure, and three-dimensional physical structure [1]. Hydrogels that range in size from tens of nanometers to several microns are known as microgels [2,3]. The nano- and micro-gels are among the various types of particles that offer numerous benefits, such as strong mechanical qualities, stability, high water content, huge flexible surface area for conjugation with a large number of cargo sealed in an aqueous environment, and biocompatibility. They are made up of polymer chains that combine to create a matrix with a high swelling capacity that can absorb and hold onto a large amount of aqueous solution [4]. Like bulky gels, microgels are typically biocompatible, but because of their smaller size, they are superior to bulky gels in many ways when utilized as biomaterials. One of the significant benefits is that, in comparison to large gels, the microgel responds to external stimuli far more quickly [5]. It is widely recognized that adding repeating units that vary from N-isopropylacrylamide (NIPAM) might alter the system's overall reaction, especially when random copolymers are included [6]. The microgels based on poly(N-isopropylacrylanide) (PNIPAM) have been studied the most. The process of free-radical precipitation polymerization makes this microgel to get easily synthesized [7]. The most significant characteristic of PNIPAM is its thermosensitive nature [8]. PNIPAM is comparatively hydrophilic at room temperature, and the microgel particles have a significant degree of swelling. For PNIPAM based microgels, the lower critical solution temperature (LCST) is also known as the volume phase transition temperature (VPTT), and this is the critical temperature. Particles shrink sharply when heated above a critical temperature because the PNIPAM polymer becomes relatively hydrophobic. Copolymerization of PNIPAM with other comonomers allows it for the adjustment of VPTT, which is approximately (32°C). PNIPAM microgels in combined form have been applied as enzyme encapsulators, drug carrier, and biosensors. The use of microgels as particulate drug carriers may shield the medications from enzymatic degradation. When compared to other particulate carriers like liposomes or micelles, PNIPAM microgels have a high degree of stability [9-12]. In this review, we have discussed the various synthesis methods and properties of microgels, and the latest advancements in drug delivery for biological and biomedical applications using microgel/nanogel particles.

2. SYNTHESIS METHODS OF MICROGELS

An extensive range of synthesis techniques have been developed because of the keen interest in microgels for a wide range of applications. One of the synthesis methods is the Bottom-up method in which smaller parts or building blocks are used to create microgels [13]. In the latter method,

monomers are usually polymerized, or polymer precursors are crosslinked in surfactant-based templates. The bottom-up method is frequently chosen because it provides better control over the essential physical characteristics of microgels. The polymerization method, which is usually based on some kind of dispersed phase free radical polymerization, directly determines the properties of the microgel. Crosslinkers and functional monomers can be easily added in different amounts to the microgel to achieve control over its functionality and porosity, which is one benefit of free radical polymerization. The free radical copolymerization is usually carried out in conjunction with precipitation polymerization for microgels based on thermoresponsive polymers, such as PNIPAM [14]. Emulsification has become one of the most popular and easy methods used for synthesis of microgels. The insolubility of expanding linear polymer chains at the polymerization temperature, which is higher than the polymer's LCST, is what propels the formation of microgels in precipitation polymerization, also known as surfactant-free emulsion polymerization **(Figure 1)**. The temperature of the aqueous solution containing surfactant, crosslinker, and monomer is raised significantly above the polymer's LCST. Propagating oligomeric radicals reach a critical chain length following the addition of the free radical initiator, at which point the polymer chain collapses and precipitates out of solution to form a precursor particle. Microgels are formed when precursor particles aggregate with other phase-separated polymer chains, typically ones that are relatively hydrophobic. Colloidal stability is provided by charged groups from the initiator, functional monomers, or surfactant. Using precipitation polymerization, aqueous microgels can be synthesized with control over crosslinking, functionality, microgel size, and particle size distribution. As an illustration, earlier research showed that the kinetic copolymerization ratios of the constituent comonomers with NIPAM can be used to accurately predict the distribution of functional monomers radially within a microgel [15]. This is consistent with the sequential centre-out mechanism of particle construction via precipitation polymerization. Moreover, precipitation polymerization can be carried out in the presence of metallic nanoparticles, polymer particles, or microgels that function as nucleation sites like the precursor particles to create more complex morphologies like core–shell microgels [16].

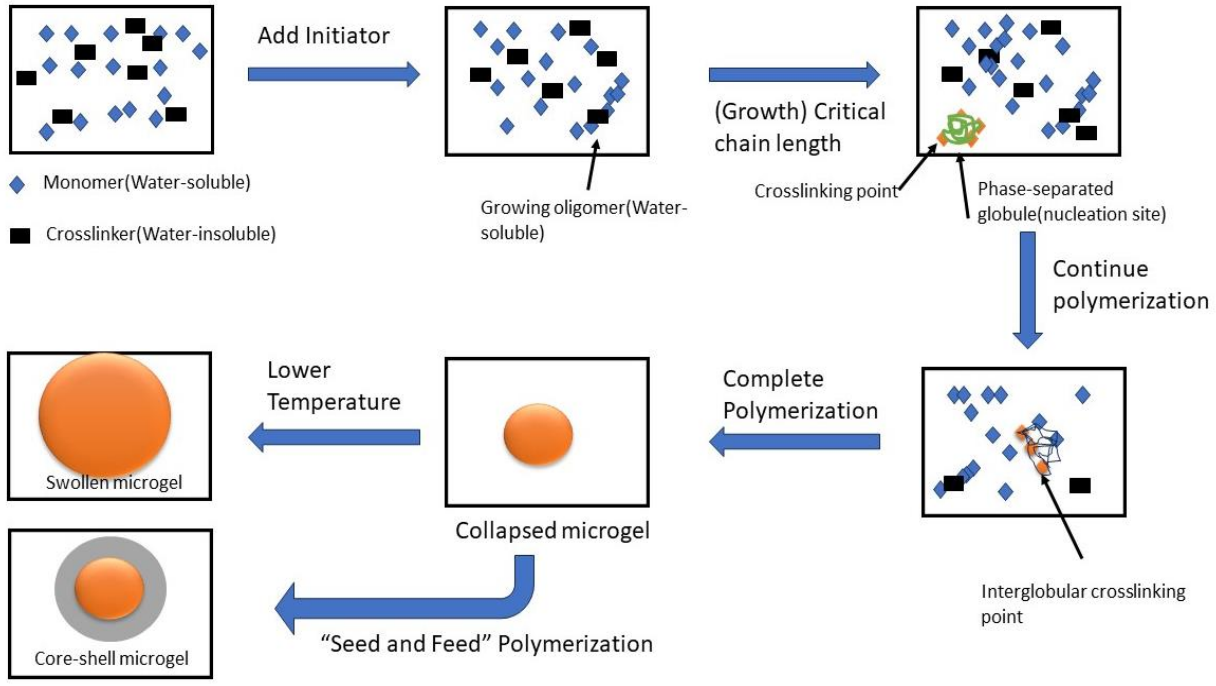

Figure 1: Schematic representation of precipitation polymerization.

Even with all its benefits, precipitation polymerization has limitation as biomacromolecule incorporation is not possible due to the high polymerization temperature, which limits the usage of only thermostable materials. Preparing nanogels, or microgels smaller than 50 nm, without the use of additional stabilizing agents is a difficult one. Moreover, free radical polymerization results in a carbon-carbon backbone devoid of a hydrolytically or enzymatically degradable linkage, meaning that only restricted control over the microgels' degradability can be applied. Lastly, the size range of the microgel is typically restricted to a small range of 100 nm < size < 1000 nm [13]. The morphology of the microgels can typically be determined by the water/oil volume ratio, emulsification rate, and polymer concentration (high concentration produces spherical microgels, low concentration produces irregular microgels). The microgel size and emulsion stability are mostly determined by the surfactant concentration. The microgels might be mechanically filtered or a stabilizing surfactant could be added during synthesis to control or limit the size range of the microgels [17]. It has been discovered that these polymerization techniques are perfectly suited for the application of living radical polymerization [18-21], providing enhanced control over the molecular architecture and degradability of microgels, as well as the ability to incorporate proteins [22] inside the microgel to increase its functionality and/or load it for later controlled release of proteins. The preparation of very small microgels (less than 50 nm) is possible with microemulsion polymerization in particular; however, this requires very high amounts of surfactant, which is difficult to fully remove, which is a major potential drawback for in vivo use. Free radical polymerization in conjunction with microfluidics provides access to spherical and nonspherical

microgels in the micrometers range. Moreover, the ability to create microgels from polymer precursors that gel upon mixing is provided by microfluidic microgel templating [23,24]. For the encapsulation of biomacromolecules and cells, microfluidics is particularly intriguing because of the large (several micron) size of the droplets and the possibility of avoiding using heat and free radicals to form the microgels [25-27].

Synthesis of PNIPAM based thermo responsive microgels

N-isopropylacrylamide is the primary monomer used for PNIPAM based microgel synthesis. It is typically obtained commercially and purified if necessary to remove any impurities that could affect the polymerization process. Crosslinkers like N, N'-methylenebisacrylamide (NMBA) are added to the monomer solution to introduce crosslinks between polymer chains, leading to the formation of a three-dimensional network structure within the microgel. Water-soluble initiators such as ammonium persulfate (APS) or potassium persulfate (KPS) are commonly used to initiate polymerization in aqueous solutions [28, 29] **(Figure 2)**. The NIPAM monomer and crosslinker are dissolved in deionized water at the desired concentration. The solution may also contain surfactants like as sodium dodecyl sulfate (SDS) or stabilizers to control particle size and prevent aggregation. The initiator (and co-initiator, if used) is added to the monomer solution, initiating the polymerization reaction. The reaction mixture is typically purged with an inert gas (e.g., nitrogen) to remove oxygen, which can inhibit polymerization. The reaction is carried out under controlled temperature conditions, usually above the LCST of PNIPAM (around 32 °C), to ensure proper polymerization and microgel formation.

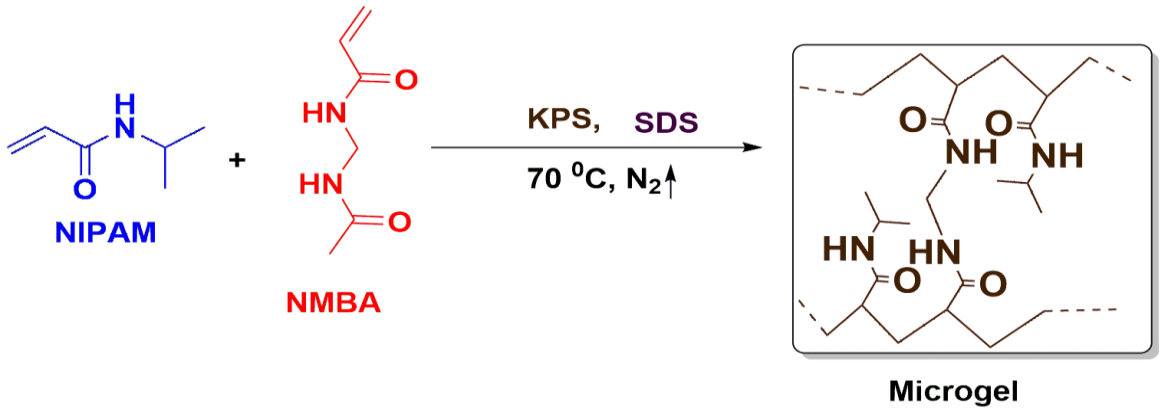

Figure 2: Schematic representation of synthesis of PNIPAM based microgel.

The reaction mixture is stirred continuously to maintain a uniform distribution of monomers, initiators, and crosslinkers throughout the solution. As polymerization proceeds, crosslinked polymer chains grow within the solution, leading to the formation of microgel particles. The growing polymer chains eventually reach a critical size where they become insoluble in the reaction solvent, causing them to precipitate out of the solution and form microgel particles. Once the desired

polymerization time is reached, the reaction is quenched, usually by cooling or by adding a quenching agent to stop further polymerization [28, 29]. The resulting microgel dispersion is then purified to remove unreacted monomers, initiators, and other impurities. Common purification methods include dialysis, ultrafiltration, or centrifugation.

3. PROPERTIES OF MICROGELS

Figure 3: Overview of properties of microgels.

Biocompatibility

The ability of a material to function in a particular application with a suitable host response is known as biocompatibility [30]. A more straightforward definition would be that a substance has no toxic effects on the body or unfavorable tissue reactions. It was reported that non-charged microgels that swell and are hydrophilic exhibit high biocompatibility [31]. However, depending on how the microgels are applied in vivo, the type of tissue such as dermal, muscular, or adipose tissue will alter the biocompatibility of the polymer used and, consequently, the immune response of the body mounts in response to the foreign substance [32]. For instance, it is well known that fibrotic scars do not form in the brain. Materials based on poly(ethylene glycol) (PEG) have been shown to induce fibrosis even though they are known to be biocompatible for in vivo applications [33]. To improve

bio-integration, biocompatible molecules like proteins are added to polymer materials to functionalize them.

Biodegradability

In most cases, once the microgels have served their purpose, the body must be cleansed of the degradation products. A microgel network can break down by oxidative/reductive, hydrolytic, enzymatic, or thermal- or photodegradation, which can be brought on, for instance, by laser radiation [34-38]. To be eliminated renally, or through the kidneys, the breakdown products that result must be smaller than 4 nm to cause the least amount of cytotoxicity and an immunological reaction, such as inflammation [39]. The chemical and internal structure of the microgel greatly influences both the molecular disintegration mechanism and the rate at which the microgel network degrades. The microgel's crosslink density and swelling capacity impact the stability of thermodynamic bonds and the rate of degradation by influencing the diffusion of the degradation trigger, such as hydrolytic enzymes, or the uptake of water, acid, or base that is necessary for hydrolysis [34]. Therefore, by employing the proper hydrophilic monomers and polymers that are exactly suited for the intended biomedical application, microgel degradation can be controlled at the molecular level [32]. Depending on the crosslinkers or degradable connectors selected, PEG-based microgels can degrade over a period of minutes to years. Consequently, the rate of degradation can be changed to suit the intended biomedical application, whether short- or long-term [34, 40, 41]. While free radical polymerization of PEG diacrylate (PEGDA) is used to enable slow degradation through ester hydrolysis at the sterically protected acrylate end-groups, a Michael-type addition between acrylate and thiol can be used for rapid degradation [40, 41]. When PEGDA and PEG diacrylamide (PEGDAA) were compared in vivo degradation experiments, PEGDA samples degraded significantly after 12 weeks, but samples made of PEGDAA showed no discernible degradation [40]. Enzyme-sensitive domains can be inserted between crosslinks in place of hydrolytically cleavable moieties to cause degradation when exposed to the appropriate enzyme [42]. Crucially, the design of the microgel's selected molecular architecture dictates the size of the degradation products. When linear molecules and star-shaped molecules have the same molecular weight, the latter will generate degradation products with smaller hydrodynamic radii that are eliminated from the body more quickly [43, 44].

Mechanical Stability

The backbone and crosslink density of the gel modifies the mechanical characteristics of the microgels, such as their softness or stiffness and, in a related sense, how they swell [32]. Additionally, the viscoelastic behavior of the microgel is determined by the type of crosslinking, which can be noncovalent, dynamic covalent, or covalent [45-48]. For example, ultrasoft, highly deformable platelet like microgels was studied for the treatment of wound-triggered haemostasis [49]. Dissipative particle dynamics simulations demonstrate that ultralow crosslinked PNIPAM microgels

(<10 kPa) cause the clot concentration to rise, thereby shortening the bleeding time [49, 50]. On the other hand, stronger microgels in the kPa to MPa range are needed in areas with higher shear forces, like the heart or the gastrointestinal tracts [51, 52].

Loading capacity

Reversible swelling behavior is a key benefit of microgels, making them ideal for encapsulating, delivering, and storing therapeutic proteins, biomacromolecules, and drug molecules [53]. Microgels can be loaded and swollen externally for delivery. Cargo is encapsulated when the loaded microgel collapses. Upon triggering the cargo release, the microgel within the body has the potential to swell again. pH, redox, light, temperature, and other chemical or physical leads can all act as triggers [54].

There following factors determine the encapsulation efficiency of the microgels:

Internal structure: The loaded molecules can diffuse more or less deeply into the microgel, depending on the network's mesh size. More molecular cargo can be absorbed by finer meshes with higher nanoporosity than by microporous microgels, suggesting that they may be better suited for encapsulating cell cargo [55-57].

Functional groups: The presence of functional groups in the microgel can improve its interaction with the specific cargo and, as a result, loading capacity. Owing to functionalization on "the inside" of the microgel, loading capacities greater than those of solid and mesoporous particles are possible because of the microgel's open network structure [58, 59].

Heterogeneity: Heterogeneity frequently manifests as a functionalization or structural gradient. During polymerization, phase separation of the building blocks or varying reaction rates can cause heterogeneity. A crosslinking gradient influences the diffusion of cargo molecules deep into the microgel, whereas a functionalization gradient restricts the capacity toward the inside or (more frequently) toward the periphery of the microgel. Conversely, diffusion may be improved by a heterogeneous polymeric network with bigger pores [60].

Microgel morphology

It would be extremely advantageous for many biomedical applications if several tasks (drug delivery, sensing, imaging, etc.) could be completed by alone nanoparticle delivery system. A microgel's outer shell could be coated with biomarkers and loaded with therapeutics, while the inner core could be loaded with quantum dots or superparamagnetic iron oxide nanoparticles (FeNP) for Magnetic resonance imaging (MRI) [61]. The development of a multicompartment microgel could offer enhanced imaging capabilities to track the residence time and successful cellular uptake of the microgel in vivo, in addition to permitting spatial and temporal control over drug release. Since no such cases have been documented to the best of our knowledge, there is a great deal of untapped research potential in this area going forward. Particle properties can be more effectively controlled with the use of multicompartment microgels [13]. For instance, the outer layer of a

multicompartment microgel, or any nanoparticle for that matter, that is exposed to the environment, controls most of its physiochemical and biological characteristics. This makes it possible to mask surfaces that, in vivo, could cause toxicity to the surrounding tissue or encourage opsonization and extravasation [62]. Microgel core-shell particles have been found to have a lower protein adsorption than other nanoparticles, which makes them especially useful for drug delivery or biomedical applications. Improved localization of chemical functionalities at the particle periphery is another benefit of core-shell morphologies. This is especially useful if the particle needs to be labelled with particular biomarkers to encourage uptake in the intended tissue.
Typically, a two-step precipitation polymerization strategy known as "seed and feed" is used to synthesize multicompartment microgels. The "seed and feed" approach call for the creation of a hydrogel layer (e.g. shell) on a seed particle (e.g. core) [63]. Like traditional precipitation polymerization, this type of polymerization is carried out at a temperature higher than the shell polymer's LCST to encourage polymer adsorption on the preexisting core particles. Organic nanoparticles like microgels or polymer particles as well as inorganic gold (AuNP) and iron (FeNP) nanoparticles can make up the core particle's chemical composition [63-70]. To impart desired functionalities for bioconjugation, drug loading, and/or degradability, the hydrogel shell's chemical composition can be controlled. Hollow capsules, core-shell, core-multishell, erodible shell, and "yolk" shell microgels are just a few of the compartmentalized microgel particles that have been created using this technique [71, 72].

Swelling behavior of microgel

PNIPAM typically exhibits the thermoresponsive behavior as shown in **Figure 4**. The particle swells and forms a soft, porous structure with its polymer networks extended at room temperature [73]. When these polymer networks are submerged in a suitable solvent, they will absorb solvent molecules until the chemical potential within and outside of the structure is equal. So, until the osmotic force exerted by the solvent is equal to the elastic forces of the crosslinks that limit swelling, swelling will continue [74]. As the temperature rises, the particle contracts and takes on a densely packed structure resembling that of a hard particle like polystyrene latex [75].

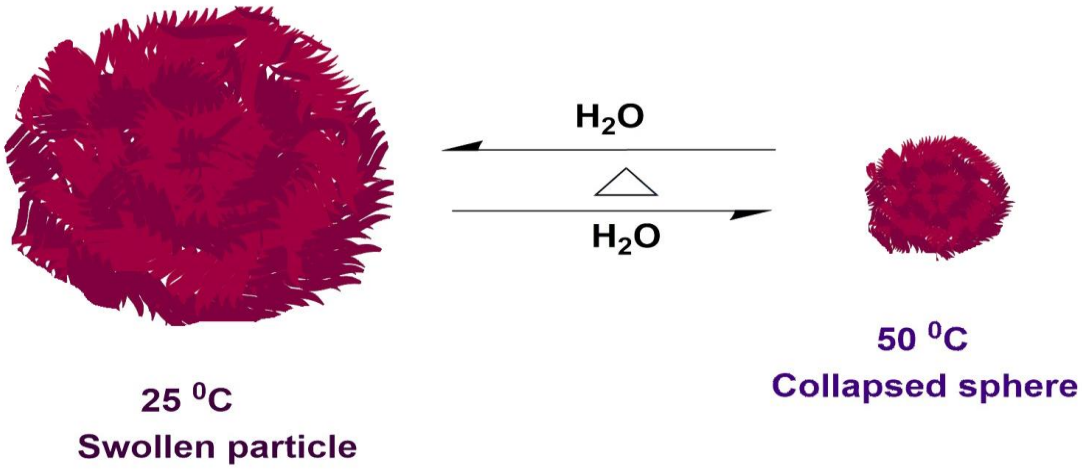

Figure 4: Illustration of typical thermoresponsive behavior of PNIPAM microgel particle.

The microgel particle size (hydrodynamic diameter) changes with temperature [73, 74, 76]. In case of NIPAM-based microgel, a significant amount of the trapped water gets expended from the pores in the polymer matrix, allowing the particle to develop on the form of a hard sphere. Due to electrostatic repulsion between charged groups on the microgel surface that originates from the initiator, the microgel particles remain dispersed while in their collapsed condition. Microgel particles shrinkage is reversible process so that on cooling back to below 34°C, the polymer–solvent interactions reform and the microgel returns to its original swollen conformation [75, 77]. The swelling behaviour is caused by the temperature dependence of hydrophobic interactions between the polymer chains and the solvent (water) as well as hydrogen bonding [78].

4. APPLICATIONS

Thermo and pH stimuli responsive microgels

Through interactions with particular ligands integrated into the network, bioactive/drug molecules can be retained in the microgels. The kinetics of diffusion through the microgel will be influenced by the binding strength of these interactions. Microgel drug release involves two step release viz., the drug first separates from the network and the drugs diffuse from the gels. Further attractive interactions between the drug and the network may occur during the second step, slowing down the diffusion rate. Certain triggers can induce and/or enhance both steps [53, 79, 80]. Apart from the diffusive release that is facilitated by numerous swollen polymer-based delivery systems, various stimuli that are biological, chemical, or physical in nature can trigger the release of an active compound or drug from the microgel [81]. Localized drug release can be induced by body temperature or external stimuli such as light and magnetic fields [82, 83]. Because of a LCST or UCST, many polymers and microgels have a cloud point [53, 84]. As a result, temperature can be used to change the microgels' state from swollen to collapsed [53, 85-87]. By altering the hydrophilic or hydrophobic nature of the microgel network, LCST and UCST can be adjusted [82]. Three polymers, namely poly(diethylacrylamide), PNIPAM, and poly(N-vinylcaprolactam) (pVCL)

are widely utilized in the formation of microgels with an LCST [82, 87]. Microgels with multiple LCSTs, such as dual-temperature responsive microgels, can be created by combining several of these polymers [88]. The selection of polymers that interact via hydrogen bonds in addition to electrostatic interactions is necessary to produce microgels with a UCST [86]. Furthermore, for the polymer to induce favorable polymer-polymer interactions below the transition temperature, a certain amount of hydrophobicity must be present in the polymer [89-90]. A lot of microgels of the UCST type, like poly(allyl urea) and poly(2-ureidoethyl methacrylate), are urea derivatives. But other composites and mixed polymer systems can also be used as UCST microgels. Combining UCST and LCST behavior, in recent years, core-shell microgels made of PNIPAM and zwitterionic sulfobetaine (SPB) have been created [91]. The poly(SPB) shell with UCST is found to swell as the temperature rose from 4 to 25 °C. The microgel's PNIPAM core collapses because of its LCST when the temperature is raised to 50 °C [91]. It was demonstrated that by adjusting the molecular weight and ratio of the component polymers, the corresponding critical temperatures could be readily adjusted [92]. Because poly-SPB is so effective at suppressing protein aggregation, this core-shell microgel approach is especially intriguing for the delivery of therapeutic proteins [93]. Additionally, this idea has been applied to the creation of temperature-responsive scaffolds and biosensing [91]. Drug delivery to tumors can be achieved by dual pH/temperature responsive PNIPAM-based self-assembled microgels functionalized with alkaline, aldehyde and hydrazide [93]. Because the pH of the microenvironment surrounding tumor cells is known to be higher than that surrounding healthy cells, study participants chosen to use PNIPAM based particles, such as poly-(N-isopropylacrylamide-co- Acrylic acid) [PNIPAM- co-PAA] microgel, as a choice for targeted cancer therapy. Furthermore, in an alkaline environment, [PNIPAM-co-PAA] swells, making it more difficult to absorb towards the cells, whereas in an acidic environment, it contracts, making absorption easier as shown in **Figure 5 [4]**. In certain tumors and inflammatory tissue with elevated temperature, temperature sensitivity allows for controlled release. The transition becomes even steeper in slightly more acidic environments [94, 95].

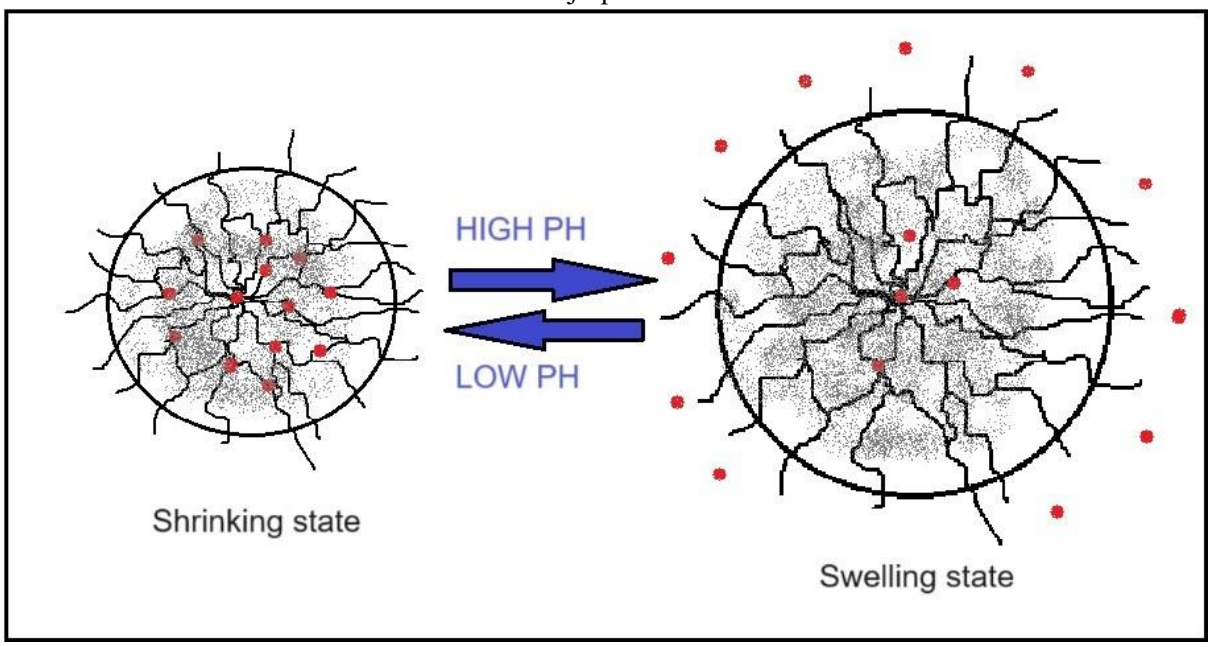

Figure 5: Drug release mechanism at different pH.

PNIPAM microgel as a drug delivery system

The benefits of hydrogels and nanoparticles are combined in PNIPAM microgels, a drug carrier. Hydrogels are known for their hydrophilicity, flexibility, high water absorptivity, and good biocompatibility [96]. On the other hand, their size in the colloidal range accounts for their long half-life in circulation and ability to be actively or passively targeted to the desired biophase, such as tumor sites. Since the reticuloendothelial system's recognition of many colloidal drug carriers is the primary cause of their removal from the blood compartment [97]. Hence the size of nanoparticle drug carriers which can be readily achieved for PNIPAM microgels should be regulated to be below 200 nm in order to prolong their blood circulation time. Solvent-filled interstitial spaces characterize the sponge-like structure of PNIPAM microgel particles. Usually, equilibrium partitioning between the solution and microgel phases can be used to load the drugs [98]. Drug loading may be significantly impacted by hydrogen bonding [99], hydrophobic interaction, and electrostatic interaction [98, 100]. The "breathing-in" technique, which involves resuspending lyophilized microgels in an aqueous drug solution is another way to load drugs [101]. The hydrogel network can fully absorb the payload, leading to a high loading efficiency. Protein/peptide medications can also be effectively transported by PNIPAM microgels. By acting as a particulate drug carrier, microgels can shield the drugs from being broken down by enzymes. One benefit of PNIPAM microgels over other particulate carriers, like liposomes or micelles, is their high stability. Protein medications may become denaturized due to particulate carriers derived from hydrophobic polymers. However, because the PNIPAM microgel is hydrophilic, this issue is avoided [96].

2. CONCLUSION

Microgels are important for developing methods for the bioavailability of advanced biopharmaceutical and biotechnological drugs at the targeted site. Microgels can encapsulate drugs and respond to environmental cues such as pH, temperature, or ionic strength. When triggered, they release the drug payload precisely where needed, minimizing side effects. These adaptable microcarriers hold great potential for improving patient outcomes in personalized medicine. The multicompartment microgels could offer enhanced imaging capabilities to track the residence time and successful cellular uptake of the microgel in vivo, in addition to permitting spatial and temporal control over drug release. There is a great deal of untapped research potential in this area going forward. PNIPAM microgel, arguably the most well-known smart soft nanomaterial, has demonstrated its adaptability in resolving a range of biomedical issues. Its adaptability is further enhanced by its capacity to be put together into more sophisticated structures. Their unique properties, including stimuli-responsive behavior and tunable network structures, make them valuable in modern medicine. Even though most of the ongoing research is still proof-of-concept, real biomedical application is anticipated in the future.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals or humans were used for the studies that are based on this research.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

ACKNOWLEDGEMENT

The authors gratefully acknowledge UGC, New Delhi, Government of India for the financial support through UGC-BSR Start-up Research Grant.

CONFLICT OF INTEREST

The authors do not have any conflict of interest.

REFERENCES

1. Hoare TR, Kohane DS. Hydrogels in drug delivery: Progress and challenges. Polym. 2008; 49:1993-2007.
2. Bhattacharya S, Eckert F, Boyko V, Pich A. Temperature-, pH-, and magnetic-field-sensitive hybrid microgels. Small. 2007; 3:650-657.
3. Karg M, Hellweg T. New “smart” poly(NIPAM) microgels and nanoparticle microgel hybrids: Properties and advances in characterization. Curr Opin Colloid Interface Sci. 2009; 14:438-450.
4. Campora S, Mohsen R, Passaro D, Samir H, Ashraf H, El-Din Al-Mofty S, et al. Functionalized

Poly(N-isopropylacrylamide)-Based Microgels in Tumor Targeting and Drug Delivery, Gels. 2021; 7:203.

5. Pelton RH, Chibante P. Preparation of aqueous latices with N-isopropylacrylamide. Colloids Surf. 1986; 20:247-256.
6. Sanzari I, Buratti E, Huang R, Tusan CG, Dinelli F, Evans ND, et al. Poly(N-isopropylacrylamide) based thin microgel films for use in cell culture applications. Nat Res Sci Rep. 2020; 10:1-14.
7. Pelton P. Temperature-sensitive aqueous microgels. Adv Colloid Interface Sci. 2000; 85:1-33.
8. Saunders RB, Laajam N, Daly E, Teow S, Hu XH, Stepto R. Microgels: From responsive polymer colloids to biomaterials. Adv Colloid Interface Sci. 2009; 147:251-262.
9. Hendrickson GR, Smith MH, South AB, Lyon AL. Design of Multiresponsive Hydrogel Particles and Assemblies. Adv Funct Mater. 2010; 20:1697-1712.
10. Hoare T, Pelton R. Characterizing charge and crosslinker distributions in polyelectrolyte microgels. Curr Opin Colloid Interface Sci. 2008;13:413-428.
11. Debord JD, Lyon A. Synthesis and Characterization of pH-Responsive Copolymer Microgels with Tunable Volume Phase Transition Temperatures. Langmuir. 2003; 19:7662-7664.
12. Smeets NMB, Hoare T. Designing Responsive Microgels for Drug Delivery Applications. Polym Chem. 2013; 51:3027-3043.
13. Suhail M, Rosenholm MJ, Minhas UM, Badshah FS, Naeem A, Khan UK, Fahad M. Nanogels as drug-delivery systems: a comprehensive overview. Ther Deliv. 2019; 10:697-717.
14. Hoare T, McLean D. Kinetic prediction of functional group distributions in thermosensitive microgels. J Phys Chem. 2006; 110:20327-20336.
15. Smith MH, Lyon LA. Multifunctional nanogels for siRNA delivery. Acc Chem Res. 2012; 45:985-993.
16. Oh KJ, Drumright R, Siegwart JD, Matyjaszewski K. The development of microgels/nanogels for drug delivery applications. Prog Polym Sci. 2008; 33:448-477.
17. Xuan L, Hou Y, Liang L, Wu J, Fan K, Lian L, et. al. Microgels for Cell Delivery in Tissue Engineering and Regenerative Medicine. Nano-Micro Lett. 2024; 16:1-42.
18. Li W, Matyjaszewski K. AGET ATRP of oligo (ethylene glycol) monomethyl ether methacrylate in inverse microemulsion. Polym Chem. 2012; 3:1813-1819.
19. Dong H, Matyjaszewski K. Thermally Responsive P(M(EO)2MA-co-OEOMA) Copolymers via AGET ATRP in Miniemulsion. Macromol. 2010; 43:4623-4628.
20. Olivera MAM, Boyer C, Nele M, Pinto CJ, Zetterlund BP, Davis PT. Synthesis of Biodegradable Hydrogel Nanoparticles for Bioapplications using Inverse Miniemulsion RAFT Polymerization. Macromol. 2011; 44:7167-7175.
21. Averick E S, Magenau DJA, Simakova A, Woodman FB, Seong ARA, Mehl AR, Matyjaszewski,

K. Covalently incorporated protein–nanogels using AGET ATRP in an inverse miniemulsion. Polym Chem. 2011; 2:1476-1478.

22. Duncanson JW, Lin, Abate AR, Seiffert S, Shah RK, Weitz DA. Microfluidic synthesis of advanced microparticles for encapsulation and controlled release. Lab Chip. 2012; 12:2135-2145.
23. Zhang H, Tumarkin E, Peerani R, Nie Z, Sullan RMA, Walker GC, Kumacheva E. Microfluidic Production of Biopolymer Microcapsules with Controlled Morphology. J Am Chem Soc. 2006; 128:12205-12210.
24. Seiffert S, Weitz DA. Microfluidic fabrication of smart microgels from macromolecular precursors. Polym. 2010; 51:5883-5889.
25. Seiffert S. Non-Spherical Soft Supraparticles from Microgel Building Blocks. Macromol Rapid Commun. 2012; 33:1286-1293.
26. Velasco D, Tumarkin E, Kumacheva E, Microfluidic encapsulation of cells in polymer microgels. Small. 2012; 8:1633-1642.
27. Kittel Y, Kuehne AJC, Laporte L D. Translating Therapeutic Microgels into Clinical Applications. Adv Healthc Mater. 2022; 11:2101989.
28. Kwon OJ, Ray DR, Siegwart DJ, Matyjaszewski K. Synthesis and biodegradation of nanogels as delivery carriers for carbohydrate drugs. Angew Chem Int Ed. 2007; 46:4830-4834.
29. Guan Y, Zhang Y. PNIPAM microgels for biomedical applications: from dispersed particles to 3D assemblies. Soft Matter. 2011; 7:6375-6384.
30. Naahidi S, Jafari M, Logan M, Wang Y, Yuan Y, Bae H, Dixon B, Chen P. Biocompatibility of hydrogel-based scaffolds for tissue engineering applications. Biotechnol Adv. 2017; 35:530-544.
31. Xue K, Wang X, Yong PW, Young DJ, Wu YL, Li Z, Loh XJ, Hydrogels as Emerging Materials for Translational Biomedicine. Adv Ther. 2019; 2:1800088.
32. Swartzlander MD, Barnes CA, Blakney AK, Kaar JL, Kyriakides TR, Bryant SJ. Linking the foreign body response and protein adsorption to PEG-based hydrogels using proteomics. Biomater. 2015; 41:26-36.
33. Bakaic E, Smeets NMB, Hoare T, Injectable hydrogels based on poly(ethylene glycol) and derivatives as functional biomaterials. RSC Adv. 2015; 5:35469-35486.
34. LeValley PJ, Neelarapu R, Sutherland BP, Dasgupta S, Kloxin CJ, Kloxin, AM, Photolabile Linkers: Exploiting Labile Bond Chemistry to Control Mode and Rate of Hydrogel Degradation and Protein Release. J Am Chem Soc. 2020; 142:4671-4679.
35. Garripelli VK, Kim JK, Namgung R, Kim WJ, Repka MA, Jo S A, Novel thermosensitive polymer with pH-dependent degradation for drug delivery. Acta Biomater. 2010; 6:477-485.
36. Hu J, Chen Y, Li Y, Zhou Z, Cheng YA. Thermo-degradable hydrogel with light-tunable degradation and drug release. Biomaterials. 2017; 112:133-144.

37. Pradhan S, Keller KA, Sperduto JL, Slater JH. Fundamentals of Laser-Based Hydrogel Degradation and Applications in Cell and Tissue Engineering. Adv Healthcare Mater. 2017; 6:1700681.
38. Alexis F, Pridgen E, Molnar LK, Farokhzad OC. Factors affecting the clearance and biodistribution of polymeric nanoparticles. Mol Pharmaceutics. 2008; 5:505-515.
39. Browning MB, Cereceres S.N, Luong PT, Cosgriff-Hernandez EM. Determination of the in vivo degradation mechanism of PEGDA hydrogels. J Biomed Mater Res. 2014; 102:4244-4451.
40. Browning MB, Cosgriff-Hernandez EM. Development of a biostable replacement for PEGDA hydrogels. Biomacromol. 2012; 13:779-786.
41. Lee DY, Choe K, Jeong YJ, Yoo J, Lee SM, Park JH, Kim P, Kim YC. Establishment of a controlled insulin delivery system using a glucose-responsive double-layered nanogel. RSC Adv. 2015; 5:14482-14491.
42. Luxenhofer R, Bezen M, Jordan R, Kinetic Investigations on the Polymerization of 2-Oxazolines Using Pluritriate Initators. Macromol Rapid Commun. 2008; 29:1509-1513.
43. Grayson SM, Godbey WT. The role of macromolecular architecture in passively targeted polymeric carriers for drug and gene delivery. J Drug Target. 2008; 16:329-356.
44. Wang CX, Utech S, Gopez JD, Mabesoone MFJ, Hawker CJ, Klinger D. Non-covalent microgel particles containing functional payloads: Coacervation of PEG-based triblocks via microfluidics. ACS Appl Mater Interfaces. 2016; 8:16914-16921.
45. Chen Y, Ballard N, Bon, SAF. Waterborne polymer nanogels non-covalently crosslinked by multiple hydrogen bond arrays. Polym Chem. 2013, 4:387-392.
46. Azuma Y, Terashima T, Sawamoto M. Precision synthesis of imine-functionalized reversible microgel star polymers via dynamic covalent cross-linking of hydrogen-bonding block copolymer micelles. Macromol. 2017; 50:587.
47. Garcia F, Smulders MMJ. Dynamic covalent polymers. J Polym Sci. 2016; 54:3551-3577.
48. Brown AC, Stabenfeldt SE, Ahn B, Hannan RT, Dhada KS, Herman ES, et.al. Ultrasoft microgels that display emergent, platelet-like behaviors. Nat Mater. 2014; 13:1108-1114.
49. Bachman H, Brown AC, Clarke KC, Dhada KS, Douglas A, Hansen CE, Herman E, et.al. Ultrasoft, highly deformable microgels. Soft Matter. 2015; 11:2018-2028.
50. Liu J, Pang Y, Zhang S, Cleveland C, Yin X, Booth L, et.al. Triggerable tough hydrogels for gastric resident dosage forms. Nat Commun. 2017; 8:124.
51. Rodell CB, MacArthur JW, Dorsey SM, Wade RJ, Wang LL, Woo YJ, et.al. Shear-Thinning Supramolecular Hydrogels with Secondary Autonomous Covalent Crosslinking to Modulate Viscoelastic Properties In Vivo. Adv Funct Mater. 2015; 25:636-644.
52. Yadav HKS, Anwar N, Halabi A, Alsalloum GA, Nanogels as Novel Drug Delivery Systems - A Review. J Pharm Res. 2017; 1:1-5.

53. Klinger D, Landfester K. Stimuli-responsive microgels for the loading and release of functional compounds: Fundamental concepts and applications. Polym. 2012; 53:5209-5231.
54. Varghese JS, Chellappa N, Fathima NN. Gelatin-carrageenan hydrogels: role of pore size distribution on drug delivery process. Colloids Surf B Biointerfaces. 2014;113:346-351.
55. Allazetta S, Lutolf MP, Stem cell niche engineering through droplet microfluidics. Curr Opin Biotechnol. 2015; 35:86-93.
56. Feng Q, Li D, Li Q, Cao X, Dong H. Microgel assembly: Fabrication, characteristics and application in tissue engineering and regenerative medicine. Bioact Mater. 2021; 9:105-119.
57. Hamzah YB, Hashim S, Rahman WA. Synthesis of polymeric nano/microgels: a review. J Polym Res. 2017; 24:134.
58. Kamperman T, Karperien M, Gac S, Leijten J. Single-Cell Microgels: Technology, Challenges, and Applications. Trends Biotechnol. 2018; 36:850-865.
59. Grimaudo MA, Concheiro A, Alvarez-Lorenzo C. Nanogels for regenerative medicine. J. Controlled Release. 2019; 313: 148-160.
60. Bae KH, Wang LS, Kurisawa M. Injectable biodegradable hydrogels: progress and challenges. J Mater Chem. 2013; 1:5371-5388.
61. Chan Y, Bulmus V, Zareie MH, Byrne FL, Barner L, Kavallaris M. Acid-cleavable polymeric core-shell particles for delivery of hydrophobic drugs. J Control Release. 2006; 115:197-207.
62. Jones CD, Lyon LA. Synthesis and characterization of multiresponsive core-shell microgels. Macromol. 2006; 33:8301-8306.
63. Blackburn WH, Lyon LA. Size-controlled synthesis of monodisperse core/shell nanogels. Colloid Polym Sci. 2008; 286:563-569.
64. Jones CD, Lyon LA. Shell-Restricted Swelling and Core Compression in Poly(N-isopropylacrylamide) Core−Shell Microgels. Macromol. 2003; 36:1988-1993.
65. Suzuki D, McGrath JG, Awaguchi H, Lyon LA. Colloidal crystals of thermosensitive, core/shell hybrid microgels. J Phys Chem. 2007; 111:5667-5672.
66. Lu Y, Ballauff M. Thermosensitive core–shell microgels: From colloidal model systems to nanoreactors. Prog Polym Sci. 2011; 36:767-792.
67. Welsch N, Becker AL, Dzubiella J, Ballauff M. Core–shell microgels as “smart” carriers for enzymes, Soft Matter. 2012; 8: 1428-1436.
68. Singh N, Lyon LA. Au Nanoparticle Templated Synthesis of pNIPAm Nanogels. Chem Mater. 2007; 19:719-726.
69. Wu S, Dzubiella J, Kaiser J, Drechsler M, Guo XH, Ballauff M. Thermosensitive Au-PNIPA yolk–shell nanoparticles with tunable selectivity for catalysis. Angew Chem Int Ed. 2012; 51:2229-2233.
70. Zhang R, Gao R, Gou Q, Lai J, Li X. Precipitation Polymerization: A Powerful Tool for

Preparation of Uniform Polymer Particles. Polym. 2022; 14: 1851

71. Hu X, Tong Z, Lyon LA. Multicompartment core/shell microgels. J Am Chem Soc. 2010; 132:11470-11472.
72. Smith MH, Herman ES, Lyon LA. Network deconstruction reveals network structure in responsive microgels. J Phys Chem. 2011; 115:3761-3764.
73. Zu S, Zhang Z, Liu Q, Wang Z, Song Z, Guo YX, Zhang S. 4D printing of core–shell hydrogel capsules for smart controlled drug release, Bio-Des Manuf. 2022; 5:294-304.
74. Chowdhry B, Kausar N, Snowden MJ. Microgels from smart polymers. Smart polym. 2008; 2:137-175.
75. Gracia LH, Snowden MJ. Preparation, properties and applications of colloidal microgels. Handbook of industrial water soluble polymers, Blackwell Publishing Ltd. 2007; 2:268-297.
76. Benee LS, Snowden MJ, Chowdhry BZ. Novel Gelling Behavior of Poly(N-isopropylacrylamide-co-vinyl laurate) Microgel Dispersions, Langmuir. 2002; 18:6025-6030.
77. Saunders BR, Vincent B. Microgel particles as model colloids: theory, properties and applications. Adv Colloid Interface Sci. 1999; 80:1-25.
78. Liu H Y, Zhu XX. Lower critical solution temperatures of N-substituted acrylamide copolymers in aqueous solutions. Polym. 1999; 40:6985-6990.
79. Martien A, Cohen, Stuart, Huck WTS, Genzer J, Muller M, Ober C, et.al. Emerging applications of stimuli-responsive polymer materials. Nat Mater. 2010; 9:101-113.
80. Garcia MC, Cuggino JC. Stimulus-responsive Polymeric Nanocarriers for Drug Delivery Applications -Types and Triggers. Biomater. 2019; 1:321–338.
81. Zha L, Banik B, Alexis F. Stimulus responsive nanogels for drug delivery. Soft Matter. 2011; 7:5908-5916.
82. Baskar V, Meeran IS, Subramani A, Sruthi, Jawahar A, Shabeer TK. Historic review on modern herbal nanogel formulation and delivery methods. Int J Pharm Pharm Sci. 2018; 10:1-10.
83. Pasparakis G, Tsitsilianis, C. LCST polymers: Thermoresponsive nanostructured assemblies towards bio applications. Polym. 2020; 211:132146.
84. Leite DC, Kakorin S, Hertle Y, Hellweg T, Silveira NP. Smart Starch-Poly(N-isopropylacrylamide) Hybrid Microgels: Synthesis, Structure, and Swelling Behavior. Langmuir. 2018; 34:10943-10954.
85. Vicario-de-la-Torre M, Forcada J. The Potential of Stimuli-Responsive Nanogels in Drug and Active Molecule Delivery for Targeted Therapy. Gels. 2017; 3:1-16.
86. Zhang Z, Li H, Kasmi S, Van Herck S, Deswarte K, Lambrecht, BN, “et. al”. A Synthetic, Transiently Thermoresponsive Homopolymer with UCST Behaviour with in a Physiologically Relevant Window. Angew. Chem. 2019; 58:7866-7872.
87. Ohshio M, Ishihara K, Maruyama A, Shimada N, Yusa SI. Synthesis and Properties of Upper

Critical Solution Temperature Responsive Nanogels, Langmuir. 2019; 35:7261-7267.

88. Kotsuchibashi Y. Recent advances in multi-temperature-responsive polymeric materials, Polym. 2020; 52:681-689
89. Shimada N, Sasaki T, Kawano T, Maruyama A, Rational design of UCST-type ureido copolymers based on a hydrophobic parameter. Biomacromol. 2018; 19:4133-4138.
90. Fujihara A, Itsuki K, Shimada N, Maruyama A, Sagawa N, Shikata T, Yusa, SI, Preparation of ureido group bearing polymers and their upper critical solution temperature in water. J Polym Sci. 2016; 54:2845-2854.
91. Rajan R, Matsumura K. Tunable Dual-Thermoresponsive core–shell nanogels exhibiting UCST and LCST Behavior, Macromol Rapid Commun. 2017; 38:1700478.
92. Rajan R, Matsumura K. A zwitterionic polymer as a novel inhibitor of protein aggregation. J Mater Chem. 2015; 3:5683-5689.
93. Mueller E, Himbert S, Simpson MJ, Bleuel M, Rheinstadter MC, Hoare T. Cationic, Anionic, and Amphoteric Dual pH/TemperatureResponsive Degradable Microgels via Self-Assembly of Functionalized Oligomeric Precursor Polymers, Macromol. 2021; 54:351-363.
94. Chanmugam A, Langemo D, Thomason K, Haan J, Altenburger EA, Tippett, "et. al". Relative Temperature Maximum in Wound Infection and Inflammation as Compared with a Control Subject Using Long-Wave Infrared Thermography. Adv Skin wound care. 2017; 30:406-414.
95. Smeets NMB, Hoare T. Designing responsive microgels for drug delivery applications. J Polym Sci. 2013; 51:3027-3043.
96. Alexis F, Pridgen E, Molnar LK, Farokhzad OC. Factors affecting the clearance and biodistribution of polymeric nanoparticles. Mol Pharm. 2008; 5:505-515.
97. Hoare T, Pelton R. Impact of Microgel Morphology on Functionalized Microgel−Drug Interactions. Langmuir, 2008; 24:1005-1012.
98. Imaz A, Forcada J. N-vinylcaprolactam-based microgels for biomedical applications. J Polym Sci Part A: Polym Chem. 2010; 48:1173-1181.
99. Bysell H, Hansson P, Malmsten M. Effect of Charge Density on the Interaction between Cationic Peptides and Oppositely Charged Microgels. J Phys Chem. 2010; 114: 7207-7215.
100. Blackburn WH, Dickerson EB, Smith MH, McDonald JF, Lyon LA, Peptide-functionalized nanogels for targeted siRNA delivery. Bioconjug Chem. 2009; 20:960-968.
101. Suhail M, Rosenholm JM, Minhas MU, Badshah SF, Naeem A, Khan KU, et.al. Nanogels as drug-delivery systems: a comprehensive overview. Ther Deliv. 2019; 10:697-717.