PREPARATION, CHARACTERIZATION AND POTENTIAL APPLICATIONS OF THERMOSENSITIVE POLYMERS- A REVIEW

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ABSTRACT
Smart polymers, also called as intelligent polymers will change their physical or chemical properties when exposed to specific minor changes like temperature, pH, and solvent, magnetic effect and pressure. Thermosensitive polymers are gaining attention nowadays as certain polymers exhibit very prominent change when exposed to body temperature. The ease of synthesis, biodegradability and ability to alter release profiles are advantageous in magnetizing researchers. In the present review, we reviewed several methods of synthesis, characterization, and potential applications in field of pharmaceutical, biopharmaceutical, medical, biotechnological and in separation and purification avenues.

Key words: Smart polymers, thermosensitive polymers, copolymerization, lower critical solution temperature.

INTRODUCTION
Smart polymers will exhibit change in their physical or chemical properties in response to specific minor changes. Based on such external stimulus these can be classified into temperature, pH, solvent, magnetic field, ions and pressure.

Of the above, thermosensitive polymers which change in response to temperature are gaining attention nowadays. These polymers undergo reversible phase transition when subjected to temperature changes. When a binary polymer solution’s liquid-liquid phase diagram at constant pressure is determined by plotting temperature of incipient phase separation as a function of concentration, called cloud point curve the minimum in this curve is precipitation threshold also called lower critical solution temperature. For example, the most widely used poly(N-isopropylacrylamide) (PNIPAAm) is a

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thermosensitive polymer that changes its macromolecular phase transition from a hydrophilic to hydrophobic structure at 32°C, called as lower critical solution temperature (LCST).\cite{9,10} Below this LCST the gel is hydrated, swollen and hydrophilic but when temperature goes above LCST, it becomes dehydrated, collapsed and hydrophobic, precipitating out from the aqueous solution.\cite{11} The critical solution temperature can be modified using surfactants like sodium cholate which increases the size of PNIPAAm with its concentration and temperature\cite{12} and by addition of hydrophilic monomers like methacrylic acid, N, N-dimethylacrylamide, N-(hydroxymethyl)-acrylamide,\cite{13} methyl 2- acetamidoacrylate.\cite{14}

**Table 1: Examples of some thermosensitive polymers**

<table>
<thead>
<tr>
<th>S. No</th>
<th>Examples of thermosensitive polymer</th>
<th>References</th>
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<tr>
<td>1.</td>
<td>Poly (N-isopropylacrylamide)</td>
<td>T. Okano et.al.\cite{15}</td>
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<td>2.</td>
<td>Poly (N-vinylcaprolactum)</td>
<td>George V. Franks et.al.\cite{16, 17}</td>
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<td>3.</td>
<td>Poly(ethoxypropylacrylamide)</td>
<td>Henna Vihola et.al.\cite{18}</td>
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<td>Poly (ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone)</td>
<td>E. Uguzdogan et.al.\cite{19}</td>
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<td>5.</td>
<td>Poly (methyl 2-acetamidoacrylate-co-methyl acrylate)</td>
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<td>Poly(organophosphazene) hydrogels</td>
<td>Hirokazu Okamura et al.\cite{14}</td>
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<td>7.</td>
<td>Poly(organophosphazenes) with lactic acid ester and methoxyethoxyethoxy side groups</td>
<td>Gyung Don Kang et.al.\cite{21}</td>
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<td>8.</td>
<td>Poly (N-isopropylacrylamide-co-methyl methacrylate-co-methacrylic acid)</td>
<td>Ahmed M. Al-Abd et.al.\cite{22}</td>
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<td>9.</td>
<td>Poly (N-isopropylacrylamide-co-hydroxyethylmethacrylate)</td>
<td>Yun Mei Bi et.al.\cite{23}</td>
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<td>10.</td>
<td>poly(N-acryloyl pyrrolidine)</td>
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<td>11.</td>
<td>Poly-(R)-N-(1-hydroxybutan-2-yl)acrylamide</td>
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<td>12.</td>
<td>PLGA-PEG-PLGA</td>
<td>You Han Bae et.al.\cite{26}</td>
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<td>13.</td>
<td>Poly N-isopropylacrylamide-polylactide copolymers</td>
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<td>14.</td>
<td>Polyvinyl acetone</td>
<td>Sibao Chen et.al.\cite{28}</td>
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<td>15.</td>
<td>Poly (N-isopropyl acrylamide-co-N-hydroxymethyl acrylamide)</td>
<td>Fiona Ni Chearui et.al.\cite{29}</td>
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<td></td>
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<td>Abdirahman saeed et.al.\cite{31}</td>
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SYNTHESIS

The various ways of synthesizing thermosensitive polymers are listed below-

**Simple polymerization**

Polymerization of N-alkylacrylamide monomers, synthesized by nucleophilic substitution of acryloyl chloride with the relevant amine results in polymer with suitable thermosensitive properties.\[19\] E.Uguzdogan et.al has synthesized temperature sensitive poly (ethoxypropylacrylamide) by solution polymerization of N-(3-ethoxypropyl)-acrylamide which was obtained by nucleophilic substitution of acryloyl chloride with 3-ethoxy-propylamine using azobisizobutyronitrile as initiator in ethanol at 70°C.\[19\]

**Copolymerization**

Lower critical solution temperature can be possessed by copolymerization with a more hydrophilic monomer or even hydrophobic monomer. Copolymerization of water soluble monomer with hydrophobic monomer will increase overall hydrophobicity thus lowering LCST while LCST can be elevated by increasing hydrophilicity.\[7\] Hirokazu Okamura et.al. synthesized poly(methyl 2- propionamidoacrylate) with geminal substituents of propionamide and methoxy carbonyl showed sharp LCST thus showing thermosensitive properties.\[32\]. He also synthesized thermosensitive polymer by copolymerization of methyl 2-acetamidoacrylate with methyl acrylate, the one obtained with 77% of the former was water soluble having thermosensitive properties.\[14\]

**Ring opening following diblock condensation**

Initially diblocks are formed then coupled with the help of coupling agent to form triblocks. Yu Tang et.al., has synthesized thermosensitive polymer to achieve controlled delivery of protein. In this Lactide and glycolide were polymerized onto monomethoxy PEG chain, the formed diblocks of monomethoxy PEG-polylactic glycolic acid were condensed and coupled with the help of coupling agent, isophorone diisocyanate and triblocks monomethoxy PEG-Poly lactic glycolic acid-monomethoxy PEG copolymer were formed. By varying the reaction initiator monomethoxy PEG and by altering the feeding ratio of lactide and glycolide monomers different block lengths of copolymers were achieved.\[33\]

**Free radical copolymerization**
Free radical copolymerization is the copolymerization in the presence of free radical ion. Kazuro L. Fujimoto et al., has carried out such a polymerization of N-isopropyl acrylamide (NIPAAm), acrylic acid (AAc) and hydroxyethyl methacrylate – poly (trimethylene carbonate) (HEMAPTMC) in the ratio of 86:4:10 at 700 C for 24 hours under argon atmosphere, exhibited thermosensitive properties. It became soluble over a period of 5 months suitable for treatment of chronic infarcted myocardium.\cite{34} Chengru Zhao et al. synthesized thermosensitive polymer using N-isopropylacrylamide and N-n-propylacrylamide with potassium sulfate and sodium sulfite as initiators.\cite{35}

**Ring opening polymerization**

Jianbo Li et al., has synthesized thermosensitive polymers using graft copolymers of N-isopropylacrylamide, N,N-dimethylacrylamide and N-(hydroxyl-methyl)acrylamide using azobisisobutyronitrile as initiator in tetrahydrofuran at 70\(^0\)C for 20 hours with ring opening polymerization of L-lactide.\cite{13}

**Surface initiated atom transfer radical polymerization**

Surface initiated atom transfer radical polymerizations of N-isopropyl acrylamide and N,N’-dimethyl aminoethyl methacrylate thermosensitivity can be incorporated into nylon membranes.\cite{36}

The same process was utilized by Nezha Badi et al. to formulate thermogels by copolymerization of 2-(2-methoxyethoxy)ethyl methacrylate and oligo(ethylene glycol)methyl ether methacrylate in 4-arm star poly (ethylene glycol) macroinitiator. The formed structures have unique property of hydrophilic core and thermosensitive outer block.\cite{37}

**Diels alder reaction**

Diels alder reaction of poly (N,N-dimethylacrylamide-co-furfuryl methacrylate) and N-[4-(formyl polyethylene glycol ester) bismaleimide, results in hydrogel having high swelling ratio and is thermosensitive in nature.\cite{38}

**Click chemistry** (Huisgen’s 1, 3-dipolar azide-alkyne cycloaddition)

It is an efficient method to control the crosslinking during polymer preparation and there is no need of restricting oxygen for the fear of oxidation, all that is required is to have starting materials in stoichiometric amounts. Jing Zhang et al., has synthesized thermosensitive hydrogel by azide modified cellulose and alkyne-modified poly (N-
isopropylacrylamide-co-hydroxyethyl methacrylate) by using copper bromide (CuBr) as a catalyst and N,N,N’,N’,N’-pentamethyldiethylenetriamine as a accelerator. The resultant hydrogel had porous network structure with thermosensitive properties.\[25\]

**CHARACTERIZATION**

There are many methods to characterize the formed polymers. Depending upon the nature of formulation certain evaluation parameters vary but, overall then they can be characterized by the following ways:

**Table 2: The basic characterization properties**

<table>
<thead>
<tr>
<th>S. No</th>
<th>Property Characterized</th>
<th>Instrument employable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Crystallinity of samples</td>
<td>Wide angle X-ray diffraction(WAXD)[39]</td>
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<td>2.</td>
<td>Morphological structure</td>
<td>Scanning electron microscopy[39,40,41]</td>
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<td>Transmission electron microscopy[42,13]</td>
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<td></td>
<td></td>
<td>FE-SEM(Field emission scanning electron microscopy)[43]</td>
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<td>3.</td>
<td>IR studies</td>
<td>FTIR[42,44,45,41]</td>
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<tr>
<td>4.</td>
<td>Particle size measurements</td>
<td>Dynamic light scattering[42,46]</td>
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<td></td>
<td></td>
<td>Laser Diffraction scattering particle size analyzer, Masterizer[46]</td>
</tr>
<tr>
<td>5.</td>
<td>Chemical composition and macromolecular weight of the polymers</td>
<td>[^1]H NMR[44]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[^13]C NMR[45,34]</td>
</tr>
<tr>
<td>6.</td>
<td>Macromolecular weight</td>
<td>Gel permeation chromatography[44,45]</td>
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<td>7.</td>
<td>Thermal properties</td>
<td>Differential scanning calorimetry[44]</td>
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<td>8.</td>
<td>State of water in swollen hydrogels</td>
<td>DSC [41]</td>
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<tr>
<td>9.</td>
<td>Measurement of mechanical properties</td>
<td>Dynamic mechanical analyzer</td>
</tr>
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Determination of LCST

The primary requisite for a polymer to be thermosensitive is to have a low LCST. It can be determined by temperature dependent transmission of the sample. Optical density of the aqueous solution is a function of temperature that can be determined using UV spectrophotometer with attached theromobath. The solutions should be heated from 23 to 45°C at a rate of 0.5°C. The critical temperature is to be taken as a point of infection of the turbidity curves.\(^\text{[42]}\)

In a constant temperature water bath the test tubes containing polymer solution should be immersed and the temperature should be altered manually, allowing the solution to adjust for 5 minutes, the phase transition can be monitored by optical transmission using UV-Visible spectrophotometer. LCST is the temperature at which 50% change in the absorbance occurs.\(^\text{[47]}\)

Cloud point measurement

a. Optical cloud point measurement

Immerse the test tubes containing polymer solution in water bath, heat at a rate of 0.2°C per minute. The temperature at which the opaqueness appears is the cloud point.\(^\text{[6]}\)

b. UV cloud point measurement

Cloud point can also be determined by noting down the original transmittance of the polymer using UV-VIS spectrophotometer while heating the cell holders by using programmable circulating bath at rate of 0.2°C per minute and the temperature indicating the 10% reduction in optical transmittance is the cloud point. The offset associated to reach the heating rate can be compensated by correction factor.\(^\text{[6]}\)

Determination of viscosity

Viscosity can be determined by using Ubbelodhe viscometer in water bath at a temperature of 20°C.\(^\text{[35]}\)

From the intrinsic viscosity the number average molecular weight can be calculated by the formula:

\[ [\eta] = kM^\alpha \]

the values of \(k\) and \(\alpha\) can be obtained from literature.

Swelling properties measurement

a. Equilibrium swelling ratio
Swelling studies are out for thermosensitive hydrogels using distilled water at various temperatures varying from 20 to 50°C and in buffer solutions with varying pH from 1.5 to 9.3 at a specific ionic strength of 0.1 mol per litre.

The equilibrium swelling ratio (ESR) can be calculated by

$$ESR = \frac{(We – Wd)}{Wd}$$

Where, $We$ and $Wd$ are weights corresponding to swollen hydrogels and dried gels. ESR should be measured after ensuring that the surface water is cleaned.\[48, 43\]

b. By gravimetric method

The degree of swelling after allowing the sample to swell in deionized water for 24 hours at varying temperatures from 15°C to 65°C can be calculated by

$$EDS(\%) = \frac{m_t}{m_0} \times 100$$

Where $m_0$ is the initial dry weight and $m_t$ is the weight of swollen film.

c. Apparent degree of swelling

Pack thermosensitive hydrogel beads in glass cylinder at 277 K. The bulk volume occupied by the beads at 277 K and after heating to 343 K should be noted. The apparent degree of swelling $S_{app}$ can be calculated from the below equation:

$$S_{app} = \frac{V_T – V_{343}}{V_{277} – V_{343}}$$

Where in $V_T$, $V_{277}$ and $V_{343}$ are volumes of hydrogel beads at 277 K and 343 K respectively.\[49\]

Deswelling kinetics measurement

Transfer the equilibrated swollen hydrogels from distilled water 24°C to 45°C and 60°C respectively. The difference in the weight is recorded after ensuring that the surface water is wiped with filter paper. Water retention can be calculated by

$$WR = 100\times \frac{(W_i – W_d)}{(W_e – W_d)}$$

Where $W_e$ is the equilibrated swollen hydrogel weight at 24°C, $W_i$ is the weight of hydrogel at regular time points and $W_d$ is the dried gel weight.\[48\]

Pulsatile kinetics of hydrogels
The pulsatile swelling behavior is observed at alternative temperatures of 20°C and 60°C in distilled water and also in buffer solution with a pH of 3.0 and 6.9. At the end of every ten minutes the weight is measured at the respective temperatures and pH values.\[48\]

**Measurement of glucose diffusion**

Glucose is used as sample analyte. Thermosensitive hydrogel slabs of defined dimensions are placed in diffusion cell side by side with glucose solution in the donor chamber and water in the receptor chamber. The solutions are kept at constant temperature and are stirred continuously to have uniformity. Then, at defined time intervals the receptor solution is analyzed to know the amount of glucose diffused.\[43\]

**Thermosensitive hydrogel degradation rate**

Degradation is directly proportional to mass loss of the hydrogel on immersing in 7 ml phosphate buffer saline at temperature of 37°C. At specific time points the relative mass loss is recorded after lyophilization. This has to be done for a period of 20 weeks.\[34\]

**Determination of gelation temperature**

a. Test tube inverting method

Thermosensitive polymer solutions of varying concentrations of 5, 10, 15, 20 and 25 wt % are prepared using deionized water. 1ml of each concentration is transferred into 4ml vial and kept at 4°C over night. Then, vials are transferred to a water bath of 15°C for 15 minutes. The sol-gel and vice versa are tested by inverting the tube in the range of 15-80°C range. The rise in temperature is at the rate of 2°C / 5minutes. The temperature at which polymer solution stops flowing is noted as gelation temperature.\[46\]

b. Falling ball method

1ml of 25% wt of polymer prepared in deionized water is placed in NMR tube with defined diameter. The time taken by a steel ball (with specific dimensions) to travel a predetermined distance is measured. The temperature is gradually increased at a rate of 2°C at each step and is equilibrated for about 20 minutes. The graph is plotted with temperature against dynamic viscosity. Dynamic viscosity is calculated using the following equation

\[\mu = (\gamma_s - \gamma_f) D^2 / (18v)\]
Where, $\mu$ is the dynamic viscosity, $\gamma_s$ and $\gamma_f$ the specific gravities of sphere and polymer solution respectively. D is the density of polymer solution and $V$ is the velocity of the falling ball.\textsuperscript{[46]}

**POTENTIAL APPLICATIONS OF THERMOSENSITIVE POLYMERS**

Thermosensitive polymers play an important role in many sectors. For the sake of convenience these applications have been classified into

- Pharmaceutical applications
- Biopharmaceutical applications
- Medical applications
- Biotechnological applications

**PHARMACEUTICAL APPLICATIONS**

**Stabilization of silver nanoparticles**

Silver nanoparticles are well known for their catalytic applications as these can serve as a bridge connecting homogenous and heterogeneous catalysis. Due to their small size and shape these nanoparticles will undergo irreversible aggregation thus creating stability problems. Zhongli et.al., has used amphiphilic poly(styrene-b-N-isopropylacrylamide) in the presence of polyethyleneimine , the linker to prevent the aggregation of silver nanoparticles which was a simpler and easier technique.\textsuperscript{[50]}

**Antifouling thermosensitive magnetic nano particles**

As both thermosensitivity and magnetism are the dual characteristics of these nano particles these are gaining importance nowadays. Unfortunately, these get adsorbed to non-specific proteins in blood plasma above LCST and will aggregate and cleared off by immune system via macrophages. Shixin Wang et.al. has coated magnetic nanoparticles applying surface free radical polymerization to polymer brushes of poly (ethylene glycol)monomethacrylate and N-(isopropylacrylamide).As a result these did not show any adsorption both at room temperature and at 45$^\circ$C.\textsuperscript{[51]}

**Thermosensitive liposomes**

Liposomes wide applications in drug delivery are hindered by its inefficient drug release. In order to overcome this limitation thermosensitive liposomes were synthesized
such that by inducing mild hyperthermia the drug can be made to release from the liposomes. Li Li et.al. has synthesized thermosensitive liposomes containing 5 mol% of 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-PEG 2000 in the lipid membrane by lipid film hydration and extrusion at 60°C. Quenched carboxyfluorescein was encapsulated in aqueous phase and 0.1% phosphatidylethanolamine-dioleoylsulfonrhodamine B was incorporated in lipid bilayer. The resultant stealth thermosensitive liposomes released drug on increasing the temperature to 42°C. With the aid of this advancement maximal intratumoral liposomal drug accumulation and rapid drug release upon triggering the temperature can be achieved.\(^{52}\)

**Thermosensitive mixed micelle gel**

The release of drug from mixed micelle gel acts as a good physical targeting specially for solid tumors. Yang yang et.al has synthesized mixed micelle gel by cold method, composing of pluronic F127 (20 %w/w) and tween 80 in the ratio of 1:6 molar ratio. The mixture was kept at 4°C overnight and mixed gently with the aid of magnetic stirrers until all pluronic granules were dissolved. Docetaxel powder was added at 4°C and was mixed for 24 hours. The release of drug from the resultant thermosensitive mixed micelle gel was sustained for more than 156 hours.\(^{53}\)

**Magnetic nanoparticles**

In an experiment conducted by S.purushotham magnetite nanoparticles were synthesized by dispersion polymerization of n-(isopropylacrylamide) chains in magnetite ferro fluid presence. The resultant composites were loaded with doxorubicin, showing thermosensitive properties. These particles have additional advantages like good magnetic properties, controlling the drug release by cycling the temperature above and below the critical solution temperature, hyperthermia attainable with low concentrations of particles, drug released in therapeutic doses promising a multimodal cancer treatment.\(^{54}\)

**Thermo sensitive magnetic liposomes**

Magnetic liposomes avail both the features of biological and physical drug targeting such that drug can be released by triggering the magnetic hyperthermia. One such liposomes were synthesized by Pallab Pradhan et.al, which are folate receptor targeted and are triggered by magnetic hyperthermia, composed of [1,2-dipalmitoyl-sn-
glycero-3-phosphocholine]: cholesterol: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)2000]:1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[(polyethylene glycol)2000] (DSPE-PEG 2000-folate) at a ratio of 80:20:4.5:0.5 molar ratio. Initially liposomes were synthesized and coencapsulated with magnetic nanoparticles and doxorubicin by a modified ammonium sulphate gradient method. The formed magnetoliposomes showed thermosensitivity, tough responsiveness to magnetic fields, thus enhancing cytotoxicity in tumor cells compared to both commercially available preparation and non-magnetic folate-targeted liposomes.[55]

In another experiment by Lin Zhu et.al., synthesized thermosensitive magnetoliposomes by reverse phase evaporation of 1,2-dipalmitoyl-sn-glycero-3-phosphocholine and cholesterol and encapsulated with methotrexate and hydrophilic magnetite-glu. The formed thermosensitive magnetoliposomes were well good both at magnetic targeting and drug release when triggered with hyperthermia.[56]

**Thermosensitive expandable Nanogels**

Yuhan Lee et.al. has synthesized nanogels which has the unique property of expanding from nano size to micro size when triggered with temperature change. The nanogels were engineered by crosslinking oligo(L-lactic acid)-poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide)-oligo (L-lactic acid) with poly ethylene glycol grafted poly(L-lysine). The 150 nanometers size of the nano gels were expanded to 1.4 micrometers when the temperature was decreased from 37°C to 15°C. The volume transition affects cell viability through a necrotic pathway because of the physical stress within the cells due to sudden spatial development.[57]

**Thermosensitive polymeric organogels**

Organogels have unique ability of loading a large amount of lipophilic drug. Low molecular weight organogels when subjected to stimuli will release drugs due to the destruction of gel network formed by hydrophobic interaction. Hideaki Tokuyama et.al. has formulated organogels by free radical copolymerization of stearyl acrylate with the aid of crosslinker, ethylene glycol dimethacrylate and accelerator, N,N,N’,N’-tetramethylethlenediamine and loaded indomethacin. Below the crystallization temperature the ordered arrangement of hydrophobic alkyl chains prevent the release of
drug but at higher temperatures the disordered amorphous structure will release the drug.\textsuperscript{[58]}

\textbf{Thermoresponsive nanofibers}

Being structurally similar to extracellular matrix nano fibers are best suited for tissue engineering. These are made by electrospinning which offer additional advantages like controllable three-dimensional structures, high porosity, and high surface area to volume ratio, thus facilitating surfaces for vascularasitation, cell migration, adhesion and proliferation. Xian Jun Loh et.al. has fabricated thermoresponsive hydrogel nanofibers based on poly(ester urethane)s encompassing poly(ethylene glycol), poly(propylene glycol) and poly(ε-caprolactone), owing to its thermosensitive nature these absorb more water under reduced temperatures and shrunk when the temperature was elevated and this behavior is exploited to control the release of protein.\textsuperscript{[59]}

\textbf{Thermosensitive hydrosomes}

Polymerosomes replace liposomes being more stable and also having the provision of modifying the surface by targeting molecules. J.S. Lee et.al. has engineered thermosensitive hydrosomes by incorporating poly(N-isopropylacrylamide) into poly(ethylene glycol)-b-poly(d,l-lactide) based polymerosomes. The resultant hydrosomes have shown release for extended four weeks with low initial burst when compared with that of polymerosomes.\textsuperscript{[60]}

\textbf{Thermosensitive transdermal release system}

Volume phase transition property of poly (N-isopropylacrylamide) is exploited to regulate the drug delivery. By turning on and off the rate controlling membrane, made of thermosensitive polymer undergoes reversible phase transition at précised temperature. When this device contacts warm skin, the membrane is impermeable as temperature is below LCST and thus the polymer is in its crystalline form but, with ailing body the temperature is enhanced that favors the membrane to turn to its amorphous form as the temperature is above LCST and permeating the drug steadily into the skin until the skin temperature returns to normal. Qiuxi Fan et.al., has engineered one such thermosensitive transdermal membrane by immobilizing poly(N-isopropylacrylamide)-co-2 mol\% acrylic acid on the surface hydrophilized poly vinylidene fluoride membrane on the inside of the membrane. Though this technique is applicable only in feverish conditions and the exact
temperature raised varies with age, it demands little more research to be carried on to finally get a thermosensitive transdermal patch.[61]

**Temperature sensitive nanotubes**

Titanate nanotubes possess unique properties like high aspect ratio, greater surface area uniform single dimensional nano channel structure but loop holes like brittleness and poor solubility in water or organic matrix and tendency to aggregate in water within short time, block their applications in biological systems. In order to overcome this limitation titanate nanotubes are functionalized with poly (N-isopropylacrylamide) through atom transfer radical polymerization. Because of the hydrophilic and hydrophobic transformations of the poly (N-isopropyl acrylamide) chains temperature switching assembly and disassembly behavior in water was observed. These nanotubes with good mechanical and thermosensitive property could be used as artificial muscles, shape memory materials and also for controlled release of the drug.[62]

**BIOPHARMACEUTICAL APPLICATIONS**

**Self assembled micelle for controlled release**

It has dual advantage of acting both by passive targeting because of its small size and active targeting with their physiochemical properties. Tianhong Qu et.al. has synthesized ABA triblock copolymer, poly(methyl methacrylate)-b-poly(N-isopropylacrylamide-co-poly(ethylene-glycol)methyl ether methacrlate)-b-poly(methyl methacrylate) employed for controlled release of the drug. The hydrophilic biocompatible long side chain poly (ethylene glycol) methyl ether methacrylate monomer into poly(N-isopropylacrylamide) raises the LCST and improves the biocompatibility of the thermo-responsive micelles. At room temperature the copolymer will assemble into “flower like” arrangement with poly (methyl methacrylate) at the core and the rest biocompatible part as shell in water. This showed remarkable thermoresponsive behavior.[63]

**Controlled release of proteins**

Growth hormone deficiency can be treated by recombinant human growth hormone but its short half life necessitates multiple injections. Thus, it’s an ideal agent for controlled release formulation. The 30% (w/v) aqueous triblock polymer, PLGA-PEG-PLGA into which porcine growth hormone was incorporated, used for controlled release.[28]
Heparin release can be controlled by controlling temperature, release rate decreases when temperature is increased above LCST. It was accomplished by preparing micro beads of alginate and hydroxypropylcellulose in the ratio of 4:1. Heparin was encapsulated in the microparticles The drug release from these beads followed 3 types primarily. Firstly, smallest heparin macromolecules whose size is less than 30nm are released. Then, the larger ones of around 60nm diffuse slowly and finally those which are larger than 60nm are released by the slow degradation of microbead structure. 

Lysozyme was delivered controllably with the help of thermosensitive polymer synthesized by modifying the structure of copolymer monomethoxy poly (ethylene-glycol)-co-poly(D,L-lactide-co-glycolide)-co monomethoxy poly(ethylene-glycol). It showed optimal aqueous solubility, sol-gel transition at 37°C, controlled both burst release and extended the release in its conformationally stable and physiologically active form thus forming the appropriate delivery system for controlled delivery of proteins.

MEDICAL APPLICATIONS

Tumor treatment

ChangJu Chun et.al. has synthesized poly(organophosphazene) – Paclitaxel conjugate by covalent ester linkage between the carboxylic acid terminated poly(organophosphazene) and the drug in the presence of Dicyclohexylcarbodiimide and dimethylaminopyridine. The aqueous solution of these conjugates was injectable, in situ forming, biodegradable that exhibited sol-gel transition upon temperature changes.

Treatment of oral mucositis

S. Rossi et.al., has synthesized mucoadhesive gel with thermosensitive properties by using trimethyl chitosan and methylpyrrolidinone chitosan. These were mixed with glycerophosphate and trimethyl chitosan in the ratio of 2:1. The gelation time was directly proportional to molecular weight of trimethyl chitosan and upon gelation best mucoadhesive properties were observed. The formulation prolonged the release of the drug (benzydamine) and overcame the physiological removal mechanisms.

Articular cartilage regeneration

Current therapies of cartilage regeneration are not successful because of low self-healing capacity of cartilage. K yung Min Park et.al. has synthesized chitosan-pluronic hydrogel by grafting pluronic onto chitosan in the presence of 1-ethyl-3-(3-
dimethylaminopropyl)-carbodiimide or N-hydroxysuccinimide. The resultant hydrogel had many advantages

- Injectable chondrocyte delivery carrier for cartilage regeneration.
- Improved mechanical properties due to its stability and biocompatibility.
- The transition time is long enough to inject the solution over 25°C though the transition to gel is around 25°C.
- The hydrogel showed more efficient chondrocyte proliferation and the extracellular matrix molecules promotion was effective compared to alginate hydrogel.
- It is minimally invasive.\(^\text{[67]}\)

**Prevention of post operative adhesions**

Post operative peritoneal adhesions are serious complications that can lead to pelvic pain, infertility and bowel obstruction. For this treatment Chang-Zheng et al., has fabricated chitosan based hydrogel barrier that can provide durable physical barrier lasting for a long period to reduce adhesion formation till the healing process is terminated. The hydrogel was formulated by chemically modifying chitosan chains by grafted hydrobutyl groups.\(^\text{[68]}\)

**BIOTECHNOLOGICAL APPLICATIONS**

**Enhanced gene delivery to the myocardium and skeletal muscle cells**

Ran Namgung et al. has synthesized multi-block copolymers from pluronic and di-(ethylene glycol) divinyl ether. This was used for the sustained and controlled delivery of plasmid DNA both in vitro as well as in vivo. The other advantages apart from controlled efficient transfection include biodegradability and site specificity.\(^\text{[69]}\)

**Thermoresponsive hydrogels in gene transfer**

The three dimensional structure of hydrogel controls the release of DNA into the surrounding muscle tissue. The controlled release of therapeutic gene enhances the duration of gene expression. Jin Sook Kwon et al., has synthesized biodegradable, thermoresponsive hydrogel for gene transfer in the heart locally. The gene expression was found to have a 4 fold increment of compared to that of naked plasmid.\(^\text{[70]}\)

**CONCLUSION**
Introduction of thermosensitive polymers has made its distinct position in drug delivery system in sustaining the release. The other advantages include its biodegradability, ease of manufacture and characterization. The biodegradable nature of these polymers provides additional benefit. These polymers have applications in many fields like pharmaceutical, biopharmaceutical, medical, biotechnological and also have spread its charm to separation and purification process. The further development would be to synthesize polymer which gets effected by two or more stimuli, though work has already started still there are miles to go and more to get from these thermosensitive polymers.
REFERENCES


47. Wangyang Lu, Baoyan Zhao, Nan Li, Yuyuan Yao, Wenxing Chen: Thermosensitive copolymer with cobalt phthalocyanine and catalytic behavior based on adjustable LCST. Reactive Functional Polymers 2010; 70: 135-41.


66. S. Rossi, M. Marcillo, M.C. Bonferoni, F. Ferrari, G. Sandri, C. Dacarro et.al: Thermally sensitive gels based on chitosan derivatives for the treatment of oral


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