REVIEW ARTICLE

Thermosensitive hydrogels: from bench to market

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Temperature-sensitive hydrogels belong to the class of 'smart hydrogels'. These hydrogels when introduced to an environment of desired temperature have the property to release the drug incorporated in them in a controlled and predictable manner. Hence, they can be used not only as a dosage form but also as a drug delivery system. Thermosensitive hydrogels due to their unique properties have wide applications in the field of biomedical science. This review summarizes various thermosensitive hydrogels that are being used, including natural as well as synthetic polymers-based hydrogels. It is important that the hydrogels have good biocompatibility and biodegradability, as well as their degradation products must be non-toxic and easily excreted out from the body. The technology of nanogels is under development that will help the hydrogels reach areas of the body otherwise difficult to reach. In essence, development of safe and efficient thermosensitive hydrogels that can be marketed and used for various ailments is the key area of research nowadays.

Keywords: Biomedical science, biocompatibility and biodegradability, synthetic polymers, thermosensitive hydrogels.

IN pharmaceutical terminology any ingredient which does not have its own biological or therapeutic activity is called a pharmaceutical excipient. Traditionally an excipient has been used only to provide weight, volume, flow properties, etc. to the active drug. However, as the field of pharmaceutical sciences evolved and developed, it demanded the excipients to be more functional for delivery of drugs and researchers focused on the use of smart biomaterials[1]. Among them, hydrogels are the most important because they offer many benefits like tuneability into many shapes and sizes, e.g. hydrogels films, beads, discs, micro and nanogels, and the ability to provide predictable and controlled release of incorporated drugs in response to a number of stimuli, e.g. heat, light, temperature, pH, UV radiation magnetic field, etc[2].

Hydrogels are included in a class of biomaterials that have 3D configuration. They are hydrophilic in nature and hence capable of retaining a large amount of water. Hydrogels have significant biomedical applications due to their 3D structure and water-retaining ability. They can be used for gene/drug delivery, tissue engineering, as carriers for encapsulation or as a barrier between different material surfaces and tissues[2].

The breakthrough in the synthesis of thermosensitive hydrogels occurred in 1970s, which led the researchers to probe the probability that chemical energy can be transferred into mechanical work. This shifted the focus from simple, macromolecular water-swollen networks into hydrogels that respond to physiological conditions of changing temperature, pH, etc.[3]. This change in environment triggers some events, such as either release of drug or formation of gel. Hydrogels are required to meet certain requirements in order to create a microenvironment inside the human body: (a) they ought to be formed by biocompatible material and their degradation products should also be biocompatible as well as biodegradable; (b) they should possess low viscosity before gelation in order to allow uniform dispersion with cells/drugs; (c) in order to circumvent toxicity and other serious reactions, the gelation rate and conditions should be proper after their injection, either *in vivo* or *in vitro*; (d) they should have sufficient strength and stability to avoid burst effect in the initial phases; (e) a steady environment, comparative to tissue strength must be maintained; (f) for the exchange of nutrients and oxygen and free cell activity, adequate porosity should be present[3].

Hydrogels can be classified into different generations. The first-generation hydrogels include those (a) which are synthesized by the polymerization of water-soluble monomers, e.g. poly(hydroxyalkylmethacrylate) hydrogels, (b) based on crosslinking of water-soluble synthetic polymers, e.g. polyvinyl alcohol (PVA) and polyethylene glycol (PEG)-based hydrogels and (c) based on cellulose. The second-generation hydrogels include (a) temperature-sensitive hydrogels, e.g. those based on PEG–polyester block copolymers, based on pNIPAAm, etc. and (b) *In situ*-forming hydrogels based on other stimuli. The third-generation hydrogels include (a) stereo complexed hydrogels and (b) hydrogels cross-linked by other physical interactions. The fourth-generation or smart hydrogels, include *in situ* chemically cross-linkable hydrogels, those

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formed by radical polymerization, double-network hydrogels, combination of natural and synthetic polymers, and composite hydrogels[4].

One of the important members of the class of smart hydrogels are the thermosensitive or temperature responsive hydrogels[5]. This effect of temperature sensitivity is due to specific monomers or polymers which gives various swelling and release at changing temperatures. Temperature change acts as a triggering factor which determines the gelling property of hydrogels regardless of any other external factors. Thermosensitive hydrogels have the added advantage of easy administration, effective drug loading and under normal physiological state they swell *in situ*[6,7]. They can be classified either as positive or negative thermosensitive systems. The positive system (with UCST, upper critical solution temperature) contracts upon cooling, whereas the negative system (with LCST, lower critical solution temperature) contracts upon heating[8]. Thermosensitive hydrogels are second-generation hydrogels[9,10].

Injectable hydrogels are yet another achievement in the hydrogel-based technology. The administered mixture of bioactive agent and gel precursor in injectable hydrogel system congeals as soon as it enters inside the body. The benefits of utilizing injectable hydrogels depend on their high flexibility (adapting to the surrounding environment), plausibility of *in vivo* conveyance in a negligibly obtrusive manner (comparatively less painful and quick recovery), and the effective and easy dosing of drugs or/and cells[3]. Injectable hydrogels, after being administered *in vivo*, lead to tissue fabrication *in situ*. This provides an opportunity to the nearby tissues to enhance their regeneration. Hence, they are used for tissue engineering and as vehicles for the delivery of genes, drugs or cells[4].

Temperature-sensitive hydrogels

The polymers, either natural or synthetic, which are used in the fabrication of temperature-sensitive hydrogels have properties which help hydrogels with regard to temperature-responsive phase transition.

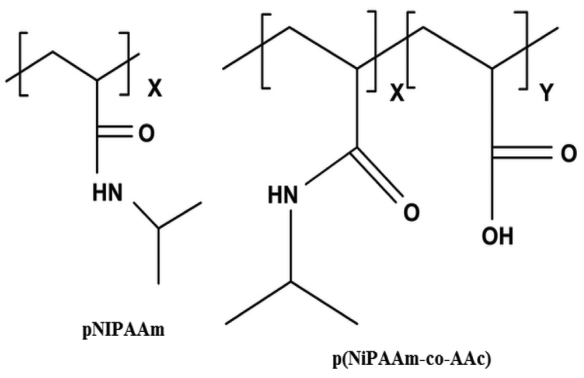

Figure 1. Structure of thermosensitive polymers units.

Figure 1 shows the general structure of NIPAAm and poly(*N*-isopropyl acrylamide-co-acrylic acid) (p(NiPAAm-co-AAc)) hydrogel polymers units. These properties are due to the presence of some functional groups as methyl, ethyl, propyl, etc. which are hydrophobic in nature. Some polymers exhibit an inverse temperature property, for example, those made up of polyethylene oxide (PEO) and polypropylene oxide (PPO). Additionally, most polymers used in the synthesis of temperature-sensitive hydrogels possess LCST which helps in easy sol–gel phase transition at body temperature[7].

Unlike most polymers, LCST polymers have less solubility with increasing temperature; this negative temperature dependence is due to the presence of both hydrophilic and hydrophobic functional groups in their structure, or only having hydrophobic groups. In such polymers, the hydrogen bonding between the polymer segments and water molecules is prominent which results in increased dissolution in water at low temperature. However, as the temperature increases, hydrophobic interactions are more strong between hydrophobic components of polymer chain which results in weak hydrogen bonding interactions; and as a result the hydrogel shrinks[8].

The thermosensitive hydrogels which act by negative thermosensitive drug release systems, have been employed to achieve switch on–switch off drug release pattern when they encounter a change in temperature[9]. The hydrogels which possess swelling at high temperature and shrinking at low temperature are known as positive-thermosensitive drug release systems. The interpenetrating network hydrogels formed by poly (acrylic acid) and polyacrylamide (PAAm) or P(AAm–co-BMA) have positive temperature dependence of swelling[10].

If the thermoresponsive hydrogels are intended to be used in parenteral form, then the polymers used must be biodegradable and there must be comprehensive elimination data available. Moreover, the cross-linker used for chemical cross-linking of thermosensitive hydrogels is mostly synthetic; the cross-linker and monomer used must be non-toxic, biocompatible and should not provoke any immunogenic response. They must not be carcinogenic or teratogenic, platelet activation by acrylamide-based polymers limits their use in clinical applications. Natural cross-linking agents from plant source are also being used, such as genipin[11,12]. They have the added advantage of not only minimal toxicity, but also, possess anti-inflammatory and antioxidant properties in order to confer survival and regeneration of cells[13,14]. CS/CSn (pDNA-BMP2)-GP, a thermosensitive chitosan hydrogel scaffold incorporated with bone morphogenetic protein-2 plasmid DNA has been used for bone repair and alveolar regeneration[12,15].

Among various types of hydrogels being developed now-a-days, thermosensitive hydrogels are discussed here with a focus on the polymers used and current work of different researchers.

Classification of thermosensitive hydrogels

Naturally derived polymer-based thermosensitive hydrogels include the following:

Chitosan-based thermosensitive hydrogels

Chitosan, derived from chitin is a polysaccharide which forms the main element of exoskeleton of various insects[7]. It is the second most naturally occurring polymer[16]. Chitosan is biodegradable, biocompatible and shows antimicrobial property[17]. Addition of glycerophosphate (GP) in chitosan makes it thermosensitive. GP leads to gel formation at high temperature by forming strong hydrogen bonds. Ruel-Gariépy *et al.*[18] synthesized chitosan glycerophosphate hydrogel that can deliver β-transforming growth factors and shows osteogenic effect. This hydrogel can also be used to clinically regenerate Ischaemic vascular disease (IVD) by seeding the former with mesenchymal stem cells[19]. Similarly, chitosan/glycerophosphate (CT/GP) gel, as mentioned above can deliver drugs such as ellagic acid for treating cancer[20]. Incorporating starch into the chitosan glycerophosphate helps in maintaining chondrocyte phenotype[21]. Grafting of pluronics on chitosan produced CTS/PEO–PPO–PEO (an injectable thermosensitive hydrogel) that caused regeneration of cartilage[22]. The efficacy and bioavailability of some ophthalmic drugs can be potentially improved using chitosan-g-poly (*N*-isopropyl acrylamide) thermosensitive gels[23]. Chitosan/GP hydrogel is not ideal in situations where fast gelation is required, as it has a long (approx. 10 min) gelation time. Derivatives of chitosan can be used to increase their solubility, such as chitosan chloride[24]. A limitation of chitosan/GP is that it causes fast release of low molecular weight drugs and proteins[25,26]. This can be controlled by mixing the drugs with liposomes and then encapsulating them with the chitosan/GP mixture[26]. Sol–gel transition temperature is not affected by the addition of liposomes[26]. Another concern regarding this system is its relative toxicity. The chitosan/GP system induces potential inflammatory response[27].

Recently, the synthesis of biopolymers (natural) as composite hydrogels is gaining importance[28–30] (Figure 2). Cartilage tissue defects can be treated by injecting chondrogenic factors with chitosan–beta glycerophosphate–hydroxyethyl cellulose (CH–GP–HEC), a biodegradable and biocompatible polymer. This provides effective treatment and the capacity of sustained release of bioactive compounds[30,31].

Thermosensitive chitosan hydrogels have been used as antioxidant components. Glutathione and ferulic acid are incorporated into the hydrogel system. They scavenge reactive oxygen species (ROS) and prevent the death of cardiomyocytes[32–34].

Chitosan grafted with PEG produces a thermoresponsive hydrogel which facilitates the delivery of bovine serum albumin (BSA) in a sustained manner[35,36]. Addition of cross-linking agents such as genipin in this mixture further enhances the sustained release profile of BSA. Other types of thermosensitive grafting include hyaluronic acid-g-chitosan-g-poly (*N*-isopropyl acrylamide)[37], chitosan-g-poly (*N*-isopropyl acrylamide[38], chitosan-g-poloxamer and pullulan-g-poly (*N*-isopropyl acrylamide-co-acrylamide)[39]. Xyloglucan is used to deliver pilocarpine hydrochloride[40].

Chitosan-based hydrogels have been shown to enhance the survival of adipose-based stem cells (ASCs) for their application in tissue engineering[24,41]. Blending chitosan with gelatin improves its biological and mechanical properties. This mixture forms a polyelectrolytic complex. Also, it mimics the environment of extracellular matrix and therefore provides suitable cell survival environment *in vitro*[42,43]. Thermosensitive chitosan hydrogel, modified by polyvinyl alcohol and glutaraldehyde, has been used to deliver the antitumour agent paclitaxel[44]. Chronic wounds can be treated using thermosensitive composite hydrogel of hydroxy butyl chitosan (CW/NPs/HBC-HG)[45].

Ophthalmic thermosensitive hydrogels, prepared by the gelation of chitosan hydrochloride have been incorporated with drugs such as β-glycerophosphate and 5-fluorouracil. This increases the bioavailability of ocular hydrogels[46].

Hyaluronic acid-based thermosensitive hydrogels

Hyaluronic acid (HA), a glycosaminoglycan (non-sulphated), consists of alternate units of glucosamine and glucuronic acid. It is widely distributed throughout the body. Its natural origin makes HA non-immunogenic, biocompatible and non-inflammatory[3]. It is directly involved in tissue organization and hence used extensively in the field of biomedical sciences such as tissue engineering and drug/gene delivery[47]. HA is modified in order to make it thermosensitive[7] (Figure 3). Conjugation of HA with PNIPAAm makes it thermosensitive, but this does not alter its characteristic of poor adhesiveness to cells[48]. Gelatin can be incorporated to improve this characteristic. This combination was found as comparable with that of brain tissue vicinity[7].

Chemical or physical modification of hyaluronic acid with thermosensitive copolymers like pluronic acid also produces hydrogels with thermosensitive properties. This copolymer helps release drugs like acyclovir in a sustained pattern[49]. Grafting of pluronic acid with HA helps in the delivery of certain antitumour drugs such as carboplatin[50].

Hyaluronic acid can be made thermosensitive by incorporating it into a poloxamer (thermosensitive block copolymer of propylene oxide and ethylene oxide). When β-transforming growth factors (TGF) conjugated with

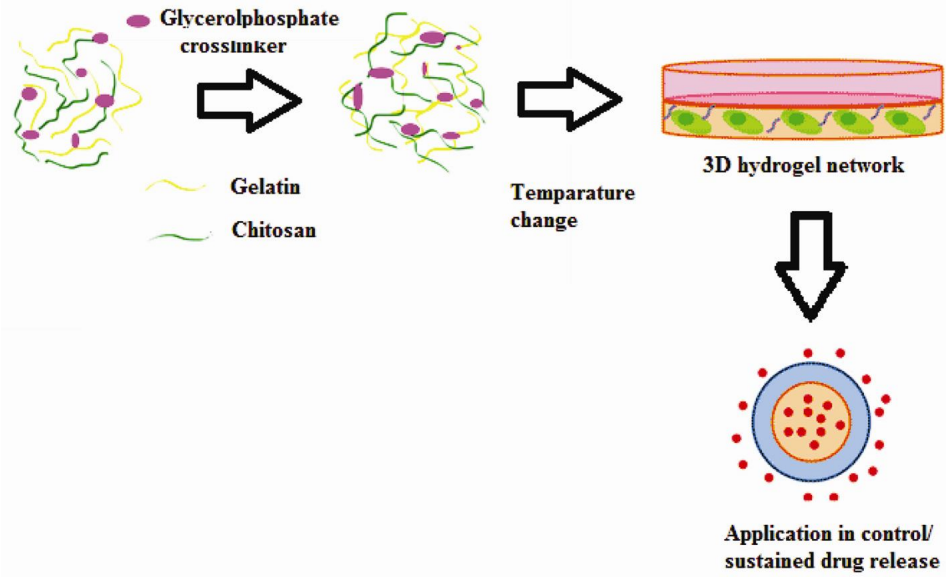

Figure 2. Schematic representation of chitosan-based thermosensitive hydrogels.

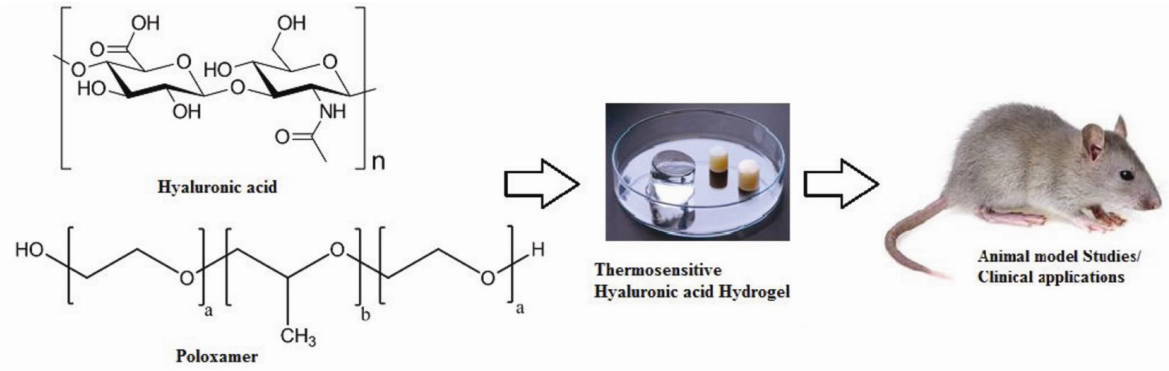

Figure 3. Thermosensitivity induction in hyaluronic acid.

heparin was mixed with hyaluronic acid poloxamer, it resulted in the release of TGF for 20 days. Upon loading of this construct on an articular cartilage, a cartilaginous contrast was formed[51]. When hyaluronic acid was grafted with a thermosensitive polymer such as PNIPAM, drugs like riboflavin showed good sustained release profile[52]. Hyaluronic acid g-poly (*N*-isopropyl acrylamide; HA-PNIPAM) coupled with PNIPAM-COOH was shown only to promote survival of human adipose cells encapsulated in it, but also maintained the morphology of human cells[53].

Hyaluronic acid ideally localizes antitumour drugs to lymph nodes. CD44 is the receptor of hyaluronic acid (primary). It is over-expressed by invasive tumour cells. For proliferation, cancer cells require high concentration of CD44 in HA[54]. Because of this selective targeting, doxorubicin is delivered intratumorally via DH700KMF-15. This is highly effective against cells with CD44 overexpression. This could potentially be used to treat metastatic cells and local tumours[55].

Cellulose-based thermosensitive hydrogels

Cellulose is the most abundant natural polymer found in plants. Cell wall of plants consists of repeating units of *β*-(1,4)-D-glucose (cellulose)[16]. It has been widely used for tissue engineering and wound healing[56]. Introduction of hydrophobic groups into cellulose makes it thermosensitive. Incorporation of alkyl groups imparts thermosensitive nature to cellulose[57], grafting of cellulose with other polymers like alginate can aid the thermosensitivity in developed formulations[58]. Methylcellulose, a derivative of cellulose, when grafted with synthetic NiPAAm (*N*-isopropyl acrylamide), showed good thermogelling properties[59]. Incorporation of microspheres loaded with lysozyme into methylcellulose thermosensitive hydrogel modified the localization and release of lysozyme[35]. Blend of hyaluronic acid and cellulose can be injected into the spinal cord[60]. Similarly, conjugation of methyl cellulose with protein laminin produces a gel which can be injected into the spinal cord (intrathecal injections) in

order to provide optimum environment for the growth of neural tissues[61].

Heparin-based thermosensitive hydrogels

Heparin, a glycosaminoglycan bearing negative charge is a highly sulphated naturally occurring polymer, present in large amounts in the liver[62]. The O and N sulphated residues of heparin interact with the lysine and arginine residues present in the growth factors. Because of this, heparin interacts with a number of growth factors and other molecules[63]. Hydrogels have three-dimensional porous structure that is able to maintain substantial quantity of water. This property of hydrogels helps in the loading and delivery of growth factors. Heparin, stabilizes the structure of hydrogel, controls the release profile and also enhances the loading of the growth factors onto the hydrogel. Heparin serves as a cofactor for bFGF and promotes its binding to receptors with high affinity, thus, increasing its activity[3]. Acidic fibroblast growth factor (aFGF) has shown protective effects in case of spinal cord injury. The major limitation in its use is the limited stability of the physico-chemical profile and the potential to cross blood–spinal cord barrier. A aFGF-loaded heparin poloxamer (aFGF-HP) thermosensitive hydrogel has been developed to provide regeneration and protection after spinal cord injury. The hydrogel system also provided increased axonal and neuronal rehabilitation[64]. Similarly, NGF-HP (nerve growth factor-heparin poloxamer) hydrogel was used for spinal cord injury. The cellular uptake of NGF was enhanced by the hydrogel without any significant toxicity. The hydrogel system worked by the inhibition of glial scar formation[65]. In case of vascular anastomosis, the recurrence of stenosis was reported to be very large. Heparin-poloxamer thermosensitive hydrogel has been found to restore the epithelial structure and function of vessel junctions that have been damaged or broken during the injury[66].

Gelatin-based thermosensitive hydrogels

Gelatin is obtained from breaking of collagen triple helix structure to single standard[67]. Because of its good biocompatibility and biodegradability, it has many applications in the biomedical field[68]. Gelatin was grafted on poly (*N*-isopropyl acrylamide; PNIPAAm), a thermosensitive polymer, via ATRP (atom transfer radical polymerization). Bone mesenchymal stem cells (BMSCs) can be delivered efficiently with this hydrogel. The injectable hydrogel is biocompatible and when delivered along with BMSCs it helps in the regeneration of bone defects[69]. Gelatin methacrylamide (gelMA) was covalently grafted onto a blend of polymers, poly(hydroxymethylglycolide-co-e-caprolactone)/poly(e-caprolactone) (PHMGCL/PCL) functionalized along with methacrylate group (pMHMGCL/PCL) via photopolymerization. This increased the strength of the hydrogel. Embedment of chondrocytes in the constructs led to stronger hybrid cartilage formation[70]. As shown in Figure 4, chitosan/gelatin/glycerol phosphate (C/G/GP) hydrogel provides sustained release of latanoprost for the treatment of glaucoma. Single-dose subconjunctival injection significantly decreased the intraocular pressure. The hydrogel also has a good hemocompatibility[71].

Chondroitin sulphate-based thermosensitive hydrogels

Chondroitin sulphate is part of ECM, which is linked to a protein throughout the body. Hence, it produce proteoglycans. It is basically a glycosaminoglycan consisting of glucuronic acid and glucosamine in alternate units. The sulphate groups present on chondroitin sulphate provide the necessary support to prevent compression of cartilage. It can be used to release growth factors[3].

Methacrylated chondroitin sulphate (CSMA) along with a thermosensitive triblock copolymer $M_{15}P_{10}$ (poly *N*-(2-hydroxypropyl) methacrylamide-mono/dilactate)-polyethylene glycol are used for the fabrication of thermo-responsive hydrogels. The hydrogel embedded with chondrogenic cells showed good porosity and can be used for 3D applications in cartilage printing[72]. Chondroitin sulphate cross-linked with F127, a thermosensitive polymer was used for cranial tissue engineering. The hydrogel construct was able to regenerate cranial cells in mice models and helped in cranial bone tissue regeneration[73]. A combination of PNIPAm with chondroitin sulphate formed a hydrogel with porous structure. This thermosensitive hydrogel is suitable for application as actuator and sensor (Figure 5). Due to internal negative charge as well as porous structure of PNIPAm/chondrotin sulphate, it is used for the controlled delivery of cationic drugs[74]. When, methacrylated *p*-HPMA-lac-PEG triblock copolymer was partially replaced by methacrylated chondroitin sulphate (CSMA), the resultant hydrogel had better thermoresponsive profile and the degradation rate was also comparatively slower[75].

Alginate-based thermosensitive hydrogels

Agarose–alginate (AA) and bio-glass-based wound dressings provide adequate environment for wound healing, i.e. moisture and angiogenesis. This hydrogel system promotes angiogenesis and helps in the migration of endothelial cells and fibroblasts. The effect of hydrogel has been successfully demonstrated on rabbit ear model. The results showed that BG/AA hydrogel can be used for healing of chronic wounds[76]. Sodium alginate-based composite thermosensitive hydrogels containing hydroxy

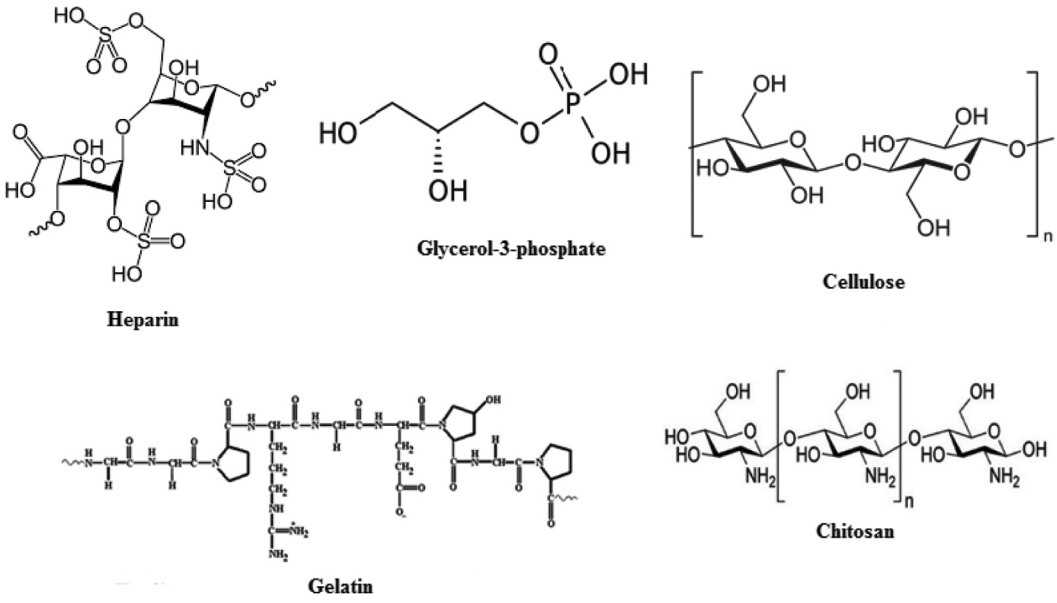

Figure 4. Chemical structure of chitosan, gelatin, glycerol phosphate, heparin and cellulose.

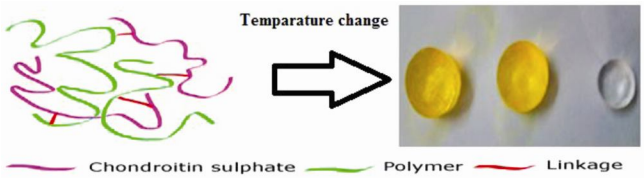

Figure 5. Chondroitin sulphate-based thermosensitive hydrogel.

methylcellulose, poloxamer 407 and iodixanol along with calcium (PSHI-Ca^2) were prepared for use in transarterial embolization. The hydrogel system indicated low levels of cytotoxicity when examined *in vitro*. Angiographic studies on tumour-induced rabbits showed that the composite hydrogel was able to successfully occlude the tumour. Hence it can be used for liver carcinomas as embolic agent[77].

Similarly, grafting of sodium alginate with amino-terminated polymers like poly(*N*-isopropyl acrylamide; PNIPAM) and PNIPAM-co-NtBAM (*n*-tertiary butyl acrylamide) copolymer synthesized via carbodiimide chemistry can result in a thermoresponsive, biodegradable injectable hydrogel[78].

Synthetic thermosensitive hydrogels include the following:

Pluronic-based thermosensitive hydrogels

These are also known as poloxamers, a copolymer of PEO–PPO–PEO (Figure 6). Antithrombotic and anti-tumour drugs have been delivered using poloxamer. Anticancer drugs such as docetaxel encapsulated in poloxamer F127 showed greater cytotoxic effect in mouse tumour models[79]. Similarly, rHV2 (recombinant hirudin variant 2), an antithrombotic agent showed good bioactivity when pluronic-127 was used as delivery vehicle[80]. The terminal hydroxyl group in pluronic-127 makes it a versatile copolymer. Chemical modification of the terminal hydroxyl group can be used to manipulate the release profile of drugs delivered via the former. Conjugation of linoleic acid into poloxamer F127 leads to sensitization of tumours[81]. The stability of pluronic copolymers is however a challenge[82]. Cross-linking of hydrogel with agents such as thiol can increase its stability; however, this affects the release profile of drugs[83]. The application of pluronic hydrogels is also limited as they are non-biodegradable[83].

Peptide-based thermosensitive hydrogels

Peptides are formed by the combination of various amino acids. Self-assembling peptides have good biocompatibility and biodegradability. Their basic unit is an oligopeptide which assembles itself in different secondary structures[84]. Doping of FEFEFKFK (phenylalanine–F, glutamic acid–E, lysine–K), an octapeptide with its thermosensitive conjugate along with PNIPAAm conjugate results in a thermosensitive hydrogel. The hydrogel gets incorporated into the peptide fibre. It has been shown that the conjugate not only enhances the mechanical properties of the hydrogel, but also helps as a triggering factor for the release of drugs[85]. Poly(ethylene glycol) poly(alanine) (mPEG-PA), a thermosensitive peptide hydrogel possesses desirable property for chondrocyte culturing and hence can be used for engineering of cartilage tissue[86].

PEG–polyester-based thermosensitive hydrogels

Linking of biodegradable polyester chains (such as polyactide, polyglycolide) to PEG makes it a biodegradable thermosensitive hydrogel[87]. A triblock copolymer, i.e. placing PEG between two polyesters provided the hydrogel with greater strength[88]. Random insertion of *p*-dioxanone into the PEG–PLA copolymer also resulted in the formation of a thermosensitive hydrogel (PLA–PDX–PEG). This hydrogel delivered BMP and led to bone regeneration[89]. A limitation of this hydrogel is that its degradable products are acids and hence can induce inflammatory response[90].

Polyacrylamide derivatives-based thermosensitive hydrogels

N-substitution of polyacrylamide renders it thermosensitive, such as PNIPAAm[91]. A large number of drugs can be delivered using this polymer. Copolymerized *N*-isopropylacrylamide with 2-hydroxy methacrylate, a monomer oligolactide, showed good encapsulation efficiency and hence was used to deliver insulin to retina[92]. Physical modification of hydrogel using porogens such as poly(dimethyl siloxane) resulted in porous hydrogels with increased protein loading capacity[93]. Like other gels, chemical cross-linking can be used to increase the stability of the hydrogel. Monomers containing double bonds are used for this purpose[7]. For example, 2-hydroxyethyl methacrylate grafted PNIPAAm was cross-linked by *N*,*N*-methylene bisacrylamide and showed good stability during glaucoma therapy[94]. The stability can also be increased by the formation of IPN (interpenetrating network). Silk fibroin/PNIPAAm IPN has shown good stability profile[95]. The major limitation in its use is that it is non-biodegradable and hence is not removed from the body. However, the hydrogel can be made degradable using segments such as PLA[96]. The fragments or products of this hydrogel can be toxic to cells, especially reproductive cells[97].

The other polymers include the POEGMA (poly(oligo (ethylene glycol) methacrylate)) hydrogels, which due to their low protein adsorption and biocompatibility are gaining popularity hydrogels in the biomedical field[98]. Chemotherapeutic drugs are being encapsulated with POEGMA hydrogel with durable drug release[7]. Polyphosphazene has alternating phosphorus and nitrogen atoms which are connected via double and single bonds. The hydrogel has good biocompatibility and its degradation products are non-toxic[99]. The property of tumour suppression makes it an excellent candidates for the delivery of anticancer agents[100]. Table 1 shows applications of hydrogels in targeting various organs.

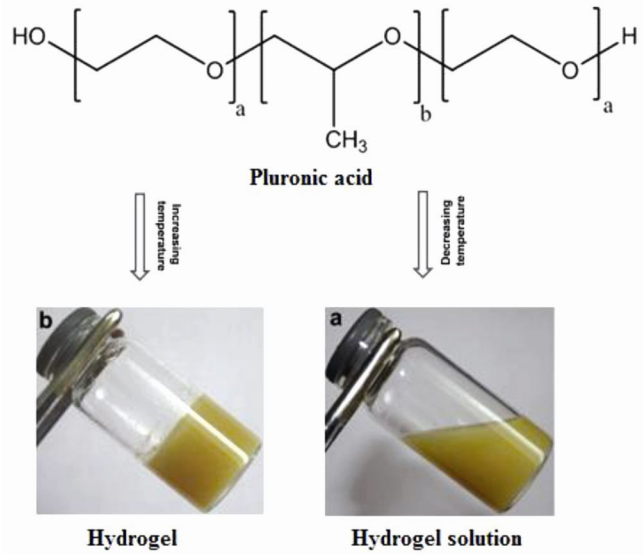

Figure 6. Response of pluronic acid (polaxomer)-based hydrogel to temperature.

Mechanism of drug release from thermosensitive hydrogels

In general, there are four basic mechanisms of drug release via a hydrogel system – (a) chemically controlled, (b) swelling controlled, (c) erosion controlled and (d) diffusion controlled[101]. The mechanism of drug release is controlled by the rate of diffusion or/and polymer degradation. In thermosensitive hydrogels, however, external temperature plays a critical role in determining the release profile. The change in the external temperature in comparison to the thermal transition temperature of hydrogels determines the release of a drug from the hydrogels. A slow release of drug is observed when the temperature is below the transition temperature. When the external temperature is raised by irradiation, etc. the drug release is also enhanced[102]. Similarly, the molecular mass of hydrogels also affects the release of drugs, where hydrogels with high molecular mass will have slow release rate. Chemical cross-linking and the use of degradable segments in hydrogels also help release the drug. The physico-chemical properties of the drug itself also affect its release. For instance, hydrophobic drugs have slower diffusion rate compared to hydrophilic drugs in the hydrogel. Thus, it is important to take into consideration the physical and chemical properties of a drug molecule in order to evaluate its release kinetics[7].

Thermosensitive hydrogels under clinical trials

The AUGMENT-HF was a randomized, prospective, international, controlled trial for evaluation of safety and benefit of use of alginate hydrogels. Alginic acid and alginates based hydrogels are used for the modification of

Table 1. Applications of hydrogels in medicine

Polymer used	Application	Target organ	Reference
Chitosan	Corneal alkali burns	Cornea (eye)	103
PLGA–PEG–PLGA	Posterior segment disorder	Eye	104
Poloxamer 407	Analgesic for skin wounds	Skin	105
CS–ASC–HGs	Tissue regeneration	Tissue	106
Pluronic F127	Neuroprotection	Brain	107
BG/AA	Chronic wound healing	Skin	108
PSHI–Ca2	Transarterial embolization	Liver	76
C/G/GP	Nucleus pulposus regeneration	Degenerated disc	77
Chondroitin sulphate	Tissue engineering	Cranial bone	42
Chitosan/gelatin	Ischaemic tissue regeneration	Tissue	73
Heparin/poloxamer	Spinal cord injury	Spinal cord	41
Hyaluronic acid	Antitumour	Colon	64

Table 2. Thermosensitive hydrogels available in the market

Polymer	Brand name	Application	Reference
Chitosan/organo phosphate	BST-Gel	Cartilage repair	109
PLGA–PEG–PLGA	ReGel	OncoGel for tumours	110
Poloxamer 407	LeGOO	Vascular injury	111
Poly(vinyl methyl ether co maleic anhydride)	Gantrez	Vaccine adjuvants	112

left ventricle in case of diseased state such as heart failure. Alginate hydrogel was injected as a permanent, inert implant into the left ventricle that serves to modify its size and shape. The therapy success rate was 35 out of a total of 40 patients. It was demonstrated that the use of alginate hydrogel along with the standard treatment regimen of chronic heart failure led to improved peak VO_2 and hence improved the overall health of individuals[113]. Cultured epithelial allograft (CEAllo) has application in terms of wound healing. Its sheets have been used to treat minor as well as major burns with effective outcomes. A thermosensitive hydrogel type CEAllo was developed and its effectiveness as well as safety determined in clinical trials phases 1 and 2. It was shown that the hydrogel was able to reconstruct/re-epithelize the tissues in case of severe second-degree burns. The trial also demonstrated that the hydrogel type allograft had no side effects[114]. Table 2 shows some market available thermosensitive hydrogels.

Future aspects

Hydrogels have evolved from a simple to a relatively complex system that is able to incorporate and release multiple agents. Recent advances in the three-dimensional hydrogel technology mimic the complex functional and biological organization of the nearby tissues. This helps to form grafts, supports the nearby cells in growth and development, and also provides strength to the organ in which they are injected. The advances in tissue engineering such as the targetted delivery of growth factors has helped overcome many diseases that were previously incurable because of inadequate methods of delivery. Smart hydrogels that respond to the physiological changes in temperature, pressure and ionic concentration are now being widely used because of their specificity. Dual gelling hydrogels provide drug delivery with minimum invasive procedures. Nanogels are hydrogels formed from nanotechnology that are able to deliver drugs to areas of the body that are usually difficult to reach. Biodegradable thermosensitive hydrogels which produce nontoxic products are now being developed. Nonetheless, new concepts in the field of hydrogels will increase their safety and efficacy as well as their performance and application in therapeutics[115].

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