INTRODUCTION

Hydrogels are water-insoluble, randomly cross-linked three-dimensional polymeric systems that have an incredible capability to swell and retain a significant amount of water within their structural framework. The water molecules entrapped into the hydrogel network crosslinks the macromolecules through physical or chemical means [1, 2]. The basic properties of hydrogels are can be brought under mechanical properties, biocompatibility properties, and swelling properties [3]. Hydrogels containing nanoparticles should be used to optimize the thermal, mechanical, optical, and chemical properties of the hydrogel [4]. Physical cross-linking of hydrogels results from weak interactions such as hydrogen bonds, hydrophilic/hydrophobic interactions, ionic/electrostatic interactions, reversible intermolecular interactions, stereo complex formation, metal coordination, π-π stacking, and polymerized entanglements. The physically cross-linked hydrogels can be easily disrupted by adding organic solvents or by changing the ionic strength, pH, or temperature owing to their weak cross-linking interaction. Chemical crosslinking results in the formation of stable hydrogel with considerable mechanical strength and are usually created by photo-polymerization; Diels-Alder clicks reaction, Michael type addition, oxime formation, Schiff base formation, and enzyme-induced crosslinks [2, 5]. Placing hydrophilic groups such as amides, sulfonic acids, hydroxyl groups, and carboxylic acids into the structure, hydrogels can absorb large amounts of water and form hydrophilic polymers [6]. It can be added through novel mechanisms that can be used to improve the physical properties of the hydrogel [7]. Hydrogels are biocompatible and biodegradable, resembling natural tissues due to their high flexibility and high moisture content. Hydrogels offer good transport properties, making them a potential drug delivery carrier to achieve targeted and prolonged-release drug delivery. Thermo-sensitive hydrogels have received considerable attention due to their ease of application, simplicity of drug formulation, less antagonistic effect on tissues, protective environment for drugs, localized drug delivery, and other attractive gelling systems [13]. Depending on thermo-sensitive groups present, the formation of thermo-sensitive hydrogels momentarily happens by a microscopic mechanism when the gelation temperature is attained. The solid phase is separated from the solution near the critical temperature [14]. Thermo-sensitive hydrogels can be classified into negatively thermo-sensitive hydrogels, dual responsive, and multi-responsive hydrogel systems.

Keywords: Thermo-sensitive hydrogels, Gelation property, Delivery of drugs, Tissue regeneration

In this review, the authors have discussed scientific advances in thermo-sensitive hydrogels over the past two decades. The ability of the thermo-sensitive hydrogel to undergo rapid changes with response to temperature makes it an attractive candidate for many biomedical applications such as targeted drug delivery, wound healing, soft contact lenses, sensors, tissue regeneration, gene, and protein delivery. This review aims to deliver a brief overview of gelation properties, merits, and demerits of various natural and synthetic thermo-sensitive polymers that have significant clinical relevance. The report emphasizes the importance of injectable thermo-sensitive hydrogels, as it can offer improved solubility of hydrophobic drugs and site-specificity, extended-release of drugs and macromolecules, improved safety, and local administration of drugs. The authors has also provided a commentary on the delivery of drugs or macromolecules from thermo-sensitive hydrogels through various approaches. This review highlights the current status of research in thermo-sensitive hydrogels and emphasizes the importance of developing nontoxic thermo-sensitive hydrogels, dual responsive, and multi-responsive hydrogel systems.

ABSTRACT

In this review, the authors have discussed scientific advances in thermo-sensitive hydrogels over the past two decades. The ability of the thermo-sensitive hydrogel to undergo rapid changes with response to temperature makes it an attractive candidate for many biomedical applications such as targeted drug delivery, wound healing, soft contact lenses, sensors, tissue regeneration, gene, and protein delivery. This review aims to deliver a brief overview of gelation properties, merits, and demerits of various natural and synthetic thermo-sensitive polymers that have significant clinical relevance. The report emphasizes the importance of injectable thermo-sensitive hydrogels, as it can offer improved solubility of hydrophobic drugs and site-specificity, extended-release of drugs and macromolecules, improved safety, and local administration of drugs. The authors has also provided a commentary on the delivery of drugs or macromolecules from thermo-sensitive hydrogels through various approaches. This review highlights the current status of research in thermo-sensitive hydrogels and emphasizes the importance of developing nontoxic thermo-sensitive hydrogels, dual responsive, and multi-responsive hydrogel systems.
delivery system depends on the temperature change to release its payload through dissolution, diffusion, disintegration, and erosion mechanism [25]. An ideal thermosensitive hydrogel drug delivery system should stream freely at ambient temperature and transform into a non-streaming gel at physiological temperature (32 °C-37 °C) [24]. This demands the development of in-situ hydrogel, which can readily arrange and harden inside the body with negligible protrusion [26]. The injectable thermosensitive hydrogel has gained special interest as it can offer improved solubility of hydrophobic metabolism and easily administered without surgical procedure [27]. Some of the limitations associated with the system include increased surgical risk associated with device implantation/retrieval and chances of clogging inside the body immediately after injection [28].

The purpose of this review is to provide an overview of thermosensitive hydrogels, important thermosensitive materials, drug delivery approaches, and applications of thermosensitive hydrogels.

Thermosensitive polymers

Thermosensitive or thermo-responsive polymers undergo macroscopic changes in the aqueous medium when lower critical solution temperature or upper critical solution temperature is reached. The thermosensitive polymers are mainly categorized into natural and synthetic polymers.

Natural polymers

Natural polymers were widely studied because of their non-toxicity, biocompatibility, biodegradability, and low inflammatory response similar to that of host tissue. However, these polymers present immunological concerns, batch to batch variation, and difficulty in purification. The natural polymers can be easily modified to obtain a wide variety of applications. Interestingly, numerous researchers obtain hydrogels by combining natural polymers with synthetic polymers. The most commonly used natural thermo-responsive polymers are categorized into polysaccharides (Cellulose derivative, Chitosan, Dextrans, Xyloglucan) and proteins (gelatin, collagen, and albumin) [29].

a. Cellulose and cellulose derivative

Cellulose is a naturally occurring water-insoluble polymer that has a greater degree of hydrophilicity on its chain structure. The insolubility of this highly hydrophilic cellulose is mainly due to the formation of strong intermolecular hydrogen bonds. The aqueous solubility of cellulose can be achieved by substitution of a certain fraction of hydroxyl groups by hydrophobic groups such as hydroxyl propyl groups or methyl groups, which in turn disrupts the intermolecular hydrogen bonds. Complete substitution of hydroxyl groups with hydrophobic moieties renders the cellulose insoluble [30]. Depending on the degree of substitution, the thermoreversibility of methycellulose can take place in the temperature range from 60 °C to 80 °C [31]. The LCST of methylcellulose hydrogels can be adjusted to physiological temperature by grafting it with other monomers. Liu et al., grafted methylcellulose with N-isopropyl acrylamide (NIPAM) in various ratios to adjust the LCST to the desired temperature [32]. The PNI-PAM grafted with lower levels of methycellulose decreased the LCST, whereas at higher levels the LCST increases. The inclusion of methycellulose into the PNI-PAM structure enhanced the mechanical stability of the gel without expulsion of the liquid. The higher LCST of cellulose derivatives limits their usage as thermo-sensitive gels. However, they are utilized as controllers to tune the other thermo-sensitive polymeric system to attain the desired LCST.

b. Chitosan

Chitosan, also known as Poliglusamis a natural poly-cationic linear oligosaccharide derived from chitin by alkaline hydrolysis. They are composed of randomly distributed acetylated and deacetylated D-glucosamine units bound with each other through 1→4 glycosidic linkages. The chitosan polymeric chains have many amine groups (–NH₂) and hydroxyl groups (–OH) [33, 34]. The amine functional group of chitosan is highly reactive and allows the derivatization of polymers for improved properties such as bio-adhesion, mucoadhesion, gene transferability, high drug loading, and controlled drug release [29, 34]. The biodegradability, biocompatibility, and low toxic potential of chitosan, make it preferable over other natural polymers [35, 33] despite their limitations such as small specific surface area and void fraction [36].

Chenite et al. (2000) were the first to explore the thermo-sensitive behavior of chitosan modified with glycerophosphate [37]. The gelation temperature remains unchanged with a varying molecular weight of chitosan, whereas it is greatly influenced by the concentration of glycerophosphate when the concentration and level of deacetylation of chitosan remain constant. The gelation temperature of the chitosan can be reduced with increasing concentration of the glycerophosphate [38, 39]. Following Chenite et al. significant advancement, several researchers were involved in the development of thermo-sensitive hydrogels on natural polymers. The mechanism of gelation involved in thermo-responsive chitosan/polyol-phosphate system has been demonstrated by Nicolas Anton et al. They stated that a hydration defensive layer of polyols is held around the chitosan through weak intermolecular hydrogen bonding; any increase in temperature disrupts the hydrogen bonding of polymer and induces gelation through stronger hydrophobic interactions [40, 41]. Bhattachar et al. produced a thermoreversible hydrogel using polyethylene glycol and chitosan without the addition of a crosslinking agent [41]. Nazar et al. synthesized N-trimethyl chitosan chloride/polyethylene glycol/glycerophosphate hydrogels for nasal drug delivery, showing thermoreversible behavior at 37 °C [42]. Though chitosan has lower mechanical strength, it is broadly utilized in the development of thermo-sensitive hydrogel systems.

c. Xyloglucan

Xyloglucan is a non-ionic hemicellulose and a hydrophilic polysaccharide that carries xylose and galactosyl-xylose. They are abundantly found in primary cell walls and seeds of all vascular plants. A "mucin-like" xyloglucan obtained from tamarind seeds are linear β-(1→4)-D-glucan chain branched with (1→6)-α-xylose or (1→2)-β-galactosyl side chains [43-45]. Xyloglucan is digested using fungal β-galactosidase to eliminate approximately 35% of the galactose residues [46, 47]. The transition temperature of xyloglucans is inversely proportional to the concentration of polymer and the percentage of galactose residues removed [48, 49]. Xyloglucans undergo a phase transition at a much lower concentration (1 to 3% wt) compared to other thermo-sensitive polymers, including block polymers [50, 51]. Xyloglucans are highly biocompatible, biodegradable, and have high water absorption/retention capacity. It has drawn a considerable research interest in developing xyloglucan hydrogels for biomedical applications [52-55]. Additionally, xyloglucan hydrogels combined with poly D-lysine showing a phase transition under physiological conditions were assessed for their possibility to deliver the cells. Poly-D-lysine-incorporated xyloglucan hydrogels promote the repair of damaged neural pathways, including the axons in the central nervous system [56]. Derivatized xyloglucans are interconnected three-dimensional microporous systems that adhere to cells and detach when the suitable temperature is reached. The microporous structure of xyloglucans directs them to be a potential delivery vehicle in the use of regenerative medication [51, 57].

d. Dextran

Dextran is a biocompatible and biodegradable polysaccharide obtained from the enzymatic decomposition of sugar cane. Dextran lacks thermosensitive behavior; however, their incorporation into other thermosensitive materials form thermosensitive hydrogels [58]. Huang et al. prepared block polymers consisting of dextran, NIPAAM, 2-hydroxyethyl methacrylate (HEMA), oligolactate that are capable of forming thermosensitive hydrogels with LCST around 32 °C. Wang et al. demonstrated the protective effects of block polymer comprising dextran, Polyacrylactone, and NIPAAm or HEMA on the remodeling of ventricular damage caused by myocardial infarction [59].

e. Gelatin

Gelatin, a thermo-reversible and cold setting polymer composed of a mixture of peptides and denatured proteins acquired by incomplete hydrolysis of collagen extracted from bones and connective tissues of animals [60]. Gelatin appears to be semi-solid beneath UCST (35 °C).
as the gelatin molecules are inter and intramolecularly crosslinked by hydrogen bonds, forming a three-dimensional triple helix steady collagen supercoil structure. The cross-linking density of the gelatin is dependent on the number of water molecules entrapped and bound to NH$_2$ groups of supercoiled chains via hydrogen bonding [61, 62]. Gelatin undergoes conformational changes from a triple helix to a random coil at 40 °C, introducing a fluidic state [61]. The fluidic state of gelatin offers a large number of reactive functional groups, allowing them for modification of gelation properties [27]. Yang and Kao developed a hydrogel composed of poly (ethylene glycol)-poly (D, L-lactide) block copolymer and gelatin, which flows effortlessly at 37 °C and remains gel at room temperature [63].

**Synthetic polymers**

Synthetic thermo-sensitive polymers are biodegradable and have a considerable mechanical strength depending on the molecular weight, concentration, and ratio of molecular units. Though the LCST of these polymers can be easily modified to the desired temperature, most of these polymers are non-biocompatible and requires the incorporation of natural polymers for their use as thermo-sensitive injectable hydrogels [59].

The various thermosensitive synthetic polymers include NIPAM-based system, PEO-PPO based system, PEG-biodegradable polyester, dimethylamino based system, poly (organophosphazene), pluronic hydrogel, PEG-polyester, Polyacrylamide derivative, 2-hydroxy ethyl dimethylamino based system, poly (organophosphazene), pluronic incorporation of natural polymers for their use as thermo-sensitive injectable hydrogels [59].

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**a. NIPAM based polymer**

N-isopropylacrylamide based hydrogels are the most widely investigated thermo-sensitive system. The homopolymer and copolymers of Poly (N-isopropyl acrylamide) (PNIPAM) are investigated for their capability to deliver drugs, encapsulate cells, and regenerate tissues. PNIPAM polymers are amphiphilic carrying amide groups (hydrophilic) and isopropyl groups (hydrophobic) with the LCST at around 32 °C. The LCST of the PNIPAM can be modified by co-polymerizing it with hydrophilic/hydrophobic monomers. Co-polymerization of PNIPAM with more hydrophilic monomers raises the LCST, whereas with more hydrophobic monomers, the LCST tends to decrease. The hydrophilic monomers such as acrylic acid and propyl acryl acid modify the LCST of PNIPAM closer to body temperature. Though PNIPAM has an increase in temperature, allowing them to be utilized as a thermo-sensitive in-situ gel matrix. PEO/PPO copolymers hydrogels attract more consideration due to their thermo-responsive behavior and biocompatibility. However, their use is limited clinically as they are non-biodegradable in vivo and need to dilute by the body fluid after infusion, which cannot be accomplished over the long term [27].

**b. PEO/PPO based systems**

Poloxamers or PEO-PPO-PEO systems or Pluronics are tri-block copolymers whose thermoreversible behavior could be manipulated by varying the composition, molecular weight, and concentration at physiological temperatures. The amphiphilic nature of this polymer is due to the presence of hydrophilic ethylene oxide moiety and hydrophobic propylene oxide moiety in the structure. The varying physicochemical properties of polyethylene and polypropylene make the poloxamer block to exhibit specific gel-like properties. The temperature rise induces a micelle formation, where the moderately hydrophilic PEO chain of the poloxamer linked with the water molecules forms a shell around the hydrophobic PPO chain wrapped into it as an inner core. However, the micelle formation is also dependent on the solution concentration. When the solution concentration exceeds the critical micelle concentration, the micelle is further entrapped, accumulated, and assembled due to various forces between the micelles. The gelation of poloxamer occurs with an increase in temperature, allowing them to be utilized as a thermo-sensitive in-situ gel matrix. PEO/PPO copolymers hydrogels attract more consideration due to their thermo-responsive behavior and biocompatibility. However, their use is limited clinically as they are non-biodegradable in vivo and need to dilute by the body fluid after infusion, which cannot be accomplished over the long term [27].

**c. PEG/PLGA based system**

Co-polymerization of polyethylene glycol (PEG) with biocompatible polyesters delivers enticing hydrogel systems. The thermosensitive behavior of the PEG/PLGA system can be modulated by altering the length of hydrophobic polyester and PEG block significantly. PLGA-PEG-PLGA tri-block copolymer has become a more fascinating thermo-sensitive material due to its in-toxicity, biocompatibility, and biodegradability. The sol-gel transition of PLGA-PEG-PLGA tri-block polymer is majorly due to the micelle formation which is driven by hydrophobic forces [73]. The biodegradability and thermo-responsive behavior of amphiphilic PEG/PLGA block copolymers have attracted special interest in the delivery of bioactive materials.

**Approaches and drug delivery system**

The thermo-sensitive hydrogels are most widely administered via subcutaneous, transdermal and mucosal routes [74-76].

**Subcutaneous drug delivery**

Unlike implants, the thermosensitive injectable hydrogels can achieve localized delivery without the requirement of invasive surgical procedures for insertion/removal of the drug delivery system. These in-situ systems release the drug in a sustained manner by undergoing a sol-gel transition at a physiological temperature [77]. If the polymer concentration is above the critical gel concentration (CGC), a gel phase will appear [78]. Subcutaneous drug delivery offers several advantages such as reduced systemic toxicity, improved patient compliance, ease in administration [79, 80]. Gong et al. synthesized a novel in-situ thermo-sensitive composite hydrogel based on PCL-PEG-PCL copolymer and pluronic F127 for the controlled release of chemotherapeutic drugs [81]. Subcutaneous delivery of thermo-sensitive PEO-PPO-PEO tri-block polymers synthesized by Cohn et al. was reported to have long-term stability and enhanced mechanical strength [82]. For successful delivery of liposomes, nanoparticles, and microspheres, an in-situ thermo-sensitive hydrogel approach would be beneficial [83]. Yang et al. demonstrated that a mixed micelle gel prepared by adding a surfactant and thermo-sensitive polymer can improve the solubility, stability, and drug release characteristics [84]. Chen et al. found that paclitaxel-loaded hydrogel released the drug over 21 d in the subcutaneous tissue and successfully suppressed tumor growth in a rat model [85]. The sol-gel transition of thermo-sensitive hydrogel given through a subcutaneous route is represented in fig. 1.
**Transdermal drug delivery**

The transdermal route is considered to be a potential site to achieve systemic delivery of drugs. The major advantages of this route include termination of drug release at any moment is possible by simple removal of the device, controlled release of a drug over a longer duration, and avoidance of first-pass metabolism [86]. The limitation of this route is, only fewer drugs satisfy the physiochemical requirements (low dose, short half-life, low molar weight, partition coefficient from 1.0 to 4.0) to permeate through the skin [87]. Gong et al. developed sustained-release in-situ curcumin loaded PEG-PCL-PEG thermosensitive hydrogel to promote wound healing [88]. The thermo-sensitive sol-gel activity helps the system to adhere to wounds at skin temperature [89].

**Ocular drug delivery**

The ocular route is the most efficient route for topical administration of drugs that can cause systemic side effects. The ocular drug delivery system offers better bioavailability and increased drug residence time [77]. The ability to deliver liquid and semi-solid dosage form via ocular route makes in-situ forming hydrogel attractive for ocular drug delivery. Cohen et al. developed a prolonged release in-situ alginate gel with higher gluconic content for ophthalmic delivery of pilocarpine, which reduces intraocular pressure over 10 h, whereas pilocarpine solution acts for the lesser duration (3 h) [86]. In vitro studies of oxytetracycline inserts on the rabbit eye showed a prolonged release of a drug over several days. Xi et al. reported a complete release of the drug (in 25 d) with Xyloglucan C loaded poloxamer P 127 and poly(tri-methylene carbonate) thermosensitive hydrogel [90].

**Rectal drug delivery**

The rectal route is considered to be the most important route for the drugs which undergo extensive first-pass metabolism. Though the administered dosage form offers considerable therapeutic efficiency in this route, the patient acceptability is poor due to the discomfort associated with the administration. The preferred dosage form for rectal administration is conventional suppositories, which are solid at room temperature and melts/softens at body temperature. The controlled release of the drug, retention of the dosage form in a specific site of the rectum, migration of dosage form upward to the colon could not be achieved with the conventional suppositories [86]. Ryu et al. reported that the bioavailability of the propranolol is increased in rats, following the incorporation of thermo-sensitive, mucoadhesive polymers like poloxamer into the conventional suppositories. Similarly, incorporation of other mucoadhesive polymers such as poly(carboxyl) and sodium alginate into suppositories increased the bioavailability of propranolol to 82.3 % and 84.7 %, respectively, with the highest mucoadhesive property and negligible intrarectal movement [91]. Xyloglucan, a thermo-sensitive gel having an intrinsic mucoadhesive property is being investigated over the past two decades for rectal administration of drugs. Xyloglucan transforms into a gel at physiological temperature. Studies showed that indomethacin-loaded xyloglucan gel administered in rabbits via rectal route have well-controlled in vivo plasma concentration and time profiles when compared to the commercial suppositories containing indomethacin without compromising the bioavailability [92].

**Sublingual drug delivery**

The sublingual route is the most promising route for the drugs which undergo extensive degradation by the gastrointestinal enzymes. In this route, the dosage form is kept beneath the tongue to deliver the drug directly into the blood vessels, thus helps in achieving high bioavailability by overcoming the first-pass metabolism [93]. The major limitations associated with this route are shorter mean residence time, smaller area for absorption, inadvertent swallowing of dosage form, and oral mucosal irritation [94]. The polymers like chitosan/dextran cross-linked with other polymers to obtain a thermosensitive hydrogel suitable for sublingual formulations [95]. Among the various polymers, PNIPAM has been extensively used in the preparation of thermo-responsive chitosan/dextran-based cross-linked copolymers for sublingual delivery [96]. Almeida et al. demonstrated the effect of temperature on drug release from thermo-responsive Ondansetron™ sublingual films. It was reported that the Ondansetron release is retarded at 37 °C compared to its release at room temperature due to the increased degree of gel cross-linking [97].

**Buccal drug delivery**

The buccal mucosa is an attractive target for the administration of the majority of pharmaceuticals [98]. The buccal mucosa is highly vascularized, thus allowing the drug to enter directly into the systemic circulation. The key benefits of buccal drug delivery include patient acceptability, cost-effectiveness, avoidance of gastrointestinal degradation, bypassing first-pass metabolism, rapid onset of action, and increased bioavailability [99]. Poloxamer, a thermo-sensitive hydrogel, has gained a special interest in buccal drug delivery owing to their sol-gel transition behavior with the response to temperature. Sandri et al. developed an in-situ thermo-sensitive buccal spray composed of poloxamer 407 (PF 127) and sodium alginate for the delivery of platelet lysate towards the treatment of oral mucositis. The poloxamer/sodium alginate spray is fluid at room temperature and rapidly forms a gel at 34 °C to 35 °C [100]. The poloxamer 407 (PF127)/polyethylene oxide (PEO) composite hydrogel showed a prolonged release of the drug. The rate at which the drug is released from the PF127/PEO system was highly dependent on the concentration of PEO. The increase in the PEO concentration retarded the drug release and the steady-state concentration is achieved [101, 102].

**Applications involved in thermosensitive hydrogel**

The thermosensitive hydrogel is a very good candidate for many biomedical applications owing to their biocompatibility and the close resemblance with the extracellular matrix. Some of the typical applications of thermo-sensitive hydrogels include tissue engineering, wound healing, soft contact lenses, and sensors. Hydrogels are widely used for complex applications such as controlled drug delivery and tissue engineering rather than simple contact lenses. Some prominent examples of thermo-sensitive hydrogels in cancer therapy, protein delivery, gene therapy, tissue regeneration, and other therapeutic areas [27, 103] are discussed as follows.

**Cancer therapy**

Traditional chemotherapeutic drugs are cytotoxic and cause systemic toxicity more often. Localized delivery of chemotherapeutic drugs in a controlled manner offers better targeting and a longer duration of action, considered to be a potential approach for the treatment of cancer. Thermosensitive hydrogels as a drug delivery agent can allow the localized administration of a chemotherapeutic drug, thereby reducing their systemic side effects and increasing their efficacy. Thermosensitive hydrogels also offer controlled release of chemotherapeutic drugs at the tumor site [104, 105]. The use of thermosensitive hydrogels in humans for cancer therapy is still under investigation. One of the major hindrances in thermosensitive hydrogel-based cancer therapy, especially with pluronics, is the dramatic change in the tumor cellular response to sensitizing the multi-drug resistance [105]. Cho et al. used thermosensitive poly (organophosphazene) as a vehicle for the controlled delivery of angiogenic inhibitor 2-methoxyestradiol to limit the oxygen and nutrient supply to the tumor cell to suppress the tumor growth [106]. Chitosan-based thermosensitive hydrogels are extensively used to deliver the chemotherapeutic and immuno-therapeutic agents for cancer treatment. Han et al. developed intra tumoral Doxorubicin and Vaccinia virus vaccine (Sig/E7/1AMP-1) loaded thermosensitive chitosan-based hydrogel for the treatment of tumor. This combination neither decreased nor increased the tumor-specific CD8+ T cells up to 60 d. The survival rate of the tumor-bearing mice was significantly increased [107].

**Tissue regeneration**

Tissue engineering has gained special attention in the field of biomedical research due to its extensive application such as regeneration of functional tissues and delivery of bioactive components including drugs and growth factors. Thermosensitive hydrogels are found to be a promising candidate for the delivery of bioactive molecules and stem/progenitor cells needed for efficient tissue regeneration [108]. A thermosensitive hydrogel that is...
capable of delivering growth factors and cells was developed by Guan et al. Angiogenesis is the most important requirement for tissue regeneration as it can ensure the nutrient/oxygen supply. Thermosensitive hydrogels are considered to be an effective delivery vehicle for angiogenic growth factors to stimulate angiogenesis in engineered tissues [189].

**Gene therapy and protein delivery**
Proteins have gained special attention due to their excellent activity. However, they are more susceptible to environmental changes such as enzymes, pH, and temperature. Thermosensitive hydrogels are widely investigated for the delivery of proteins and growth factors due to their ability to control, sustain, and achieve optimal doses at local sites for effective tissue regeneration and repair. Thermosensitive hydrogels, a carrier for the protein delivery has several advantages such as uniform dispersion of protein in three-dimensional networks to prevent aggregation, precipitation, and inactivation, avoidance of denaturation of proteins during preparation, storage, and delivery by denaturation of proteins during preparation, storage, and delivery by forming a protective layer to isolate it from environment, and controlled/sustained release of proteins [110]. Chen et al. developed vascular endothelial growth factor (VEGF) loaded injectable thermosensitive poly (D, L-lactic-co-glycolic acid)-b methoxy poly (ethylene glycol) (PLGA-MPEG) hydrogel for inducing neovascularization and bone regeneration [111].

**Other application of thermosensitive hydrogels**
Thermosensitive hydrogels have enormous potential in several applications including wound care, cosmetology, etc. Intranasal delivery of thermosensitive hydrogels offers efficient systemic drug delivery and has the potential to bypass the blood-brain barrier by altering the permeability in the nasal cavity [112, 113]. Thermosensitive hydrogel allows heat dissipation, mimicking the biological sweating phenomenon [114]. Thermosensitive hydrogels are excellent carriers for the delivery of various biotherapeutic molecules as it can protect the incorporated cells and release them in a controlled manner [27].

**Table 1: Summary of various thermosensitive hydrogels**

| Methods                     | Polymers          | Drugs            | Formulation | Treatment       | Reference |
|-----------------------------|-------------------|------------------|-------------|-----------------|-----------|
| Thin-layer evaporation      | Chitosan, Poloxamer | Opiophin         | Liposomes   | Liver cancer    | [115]     |
| Ammonium sulfite sodium method | Carbopol, HPMC   | Dextrorubicin    | Liposomes   | Liver cirrhosis | [116]     |
| Emulsion evaporation method | Chitosan, gelatin| Curcumin         | Nanoparticle | Glaucoma        | [117]     |
| Melt emulsification method  | MPEG-PCL          | Docetaxel        | Nanoparticle | Anti-ovarian cancer | [118] |
| Emulsification and solvent diffusion method | HPMC, Pluronic F 127 | Sertoconazole | Nanostructured | Fungal keratitis | [119] |
| Hot emulsification method   | Chitosan          | Methotrexate     | Nanotubes   | Control tumor cell growth | [120] |
| Ethanol injection method    | Poloxamer 407, HPMC K100, Carbopol 934 | Zolmitriptan | Nanoothemoses | Treat headache disorders | [121] |
| Simple thin-film method     | Pluronic F-127 and Pluronic L 121 | Dextorubicin and Docetaxel | Micelles | Treat tumor | [122] |
| Rotary evaporation sonication technique | Pluronic F-127 | Insulin | Transfersomes | Treat diabetes mellitus | [123] |
| Emulsion cross-linking method | Chitosan, PF-127 | Lorazepam | Microsphere | Treat epilepsy | [124] |
| Fluorescence imaging method | Amphiphilic co-polymer | Pachtalex | Free drug | Intraperitonal chemotherapy of carcinomatosis | [125] |
| Wang’s method               | Hydroxy-buty1 chitosan | Dopamine | Free drug | Hemostasis | [126] |

**CONCLUSION**
Thermo-sensitive hydrogels based on natural and synthetic polymers exhibit lower critical solution temperature, low inflammatory response, biocompatibility, biodegradability, and mechanical properties suitable for various applications such as cancer therapy, protein delivery, gene delivery, tissue regeneration, and wound care. The route of administration and physiochemical properties of the drug has an important effect on the selection of thermo-sensitive polymers. Commercially available and FDA approved PF-127 is the most used thermo-sensitive polymer to date. Evidence from various in vitro and in vivo studies showed that existing thermo-sensitive hydrogels exhibit reduced cell viability and reduced capability to deliver the cells to the target tissues. However, with the appropriate experimentation, these limitations could be easily addressed. On the other hand, the properties of thermo-sensitive hydrogel should be improved to enable its usage in clinical practice.

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Declared none

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