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*Review article*

# Thermosensitive hydrogel: an inventive carrier for drug delivery

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**ABSTRACT**

Hydrogels are water-swollen polymeric materials able to maintain a distinct three dimensional structure. They were the first biomaterials designed for clinical use in the early 1950s, when Otto Wichterle and Drahoslav Lím initiated a research program aimed to the development of hydrogels for soft contact lenses. The fortunate use of hydrogels in ophthalmology, which translated, besides contact lenses, also in glaucoma micro capillary drains and fillings for the restoration of detached retina, was the driving force towards the exploration of many other biomedical applications. Indeed, hydrogels extended their use to coverings for perforated ear drums, implants for plastic surgery, drug delivery depots, etc. Amazingly, after 60 years, hydrogels are still inspiring the scientific community and progress in this field has moved forward at an impressive pace. Nowadays, novel synthetic methods for the design of gel-forming polymers and molecular biology have encompassed traditional chemical methods, resulting in self-assembling and environmentally sensitive hydrogels with controlled degradability and mechanical properties. Hydrogels have been applied, in addition to traditional areas, also to the delivery of biotechnologically derived drugs (proteins and peptides), tissue engineering, micro fluidics and nanotechnology. The success of hydrogels originates from their well known biocompatibility mainly due to their high water content and soft nature. These properties render hydrogels similar to biological tissues and consequently minimize cell adherence and inflammation once injected or implanted in the body. Furthermore, their water absorbing capacity facilitates the accommodation of cells or hydrophilic molecules such as protein and peptides within the polymeric network.

## 1. Introduction

Controlled drug delivery systems, which are intended to deliver drugs at predetermined rates for predefined periods of time, have been used to overcome the shortcomings of conventional drug formulations. Although significant progress has been made in the controlled drug delivery area, more advances are yet to be made for treating many clinical disorders, such as diabetes and rhythmic heart disorders. In these cases, the drug has to be delivered in response to fluctuating metabolic requirements or the presence of certain biomolecules in the body. In fact, it would be most desirable if the drugs could be administered in a manner that precisely matches physiological needs at proper times (temporal modulation) and/or at the proper site (site-specific targeting). In addition, the controlled drug delivery area needs further development of techniques for delivery of peptide and protein drugs. In the body, the appearance of numerous bioactive peptides is tightly controlled to maintain a normal metabolic balance via a feedback system called 'homeostasis'[1]. It would be highly beneficial if the active agents were delivered by a system that sensed the signal caused by disease, judged the magnitude of signal, and then acted to release the right amount of drug in response. Such a system would require coupling of the drug delivery rate with the physiological need by means of some feedback mechanism. Hydrogels have been used extensively in the development of the smart drug delivery systems. A hydrogel is a network of hydrophilic polymers that can swell in water and hold a large amount of water while maintaining the structure. A three-dimensional network is formed by crosslinking polymer chains. Crosslinking can be provided by covalent bonds, hydrogen bonding, van der Waals interactions, or physical entanglements[7]. Hydrogels can protect the drug from hostile environments, e.g. the presence of enzymes and low pH in the stomach. Hydrogels can also control drug release by changing

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the gel structure in response to environmental stimuli. Hydrogels containing such 'sensor' properties can undergo reversible volume phase transitions or gel–sol phase transitions upon only minute changes in the environmental condition. The types of environment-sensitive hydrogels are also called 'Intelligent' or 'smart' hydrogels[6]. Many physical and chemical stimuli have been applied to induce various responses of the smart hydrogel systems. The physical stimuli include temperature, electric fields, solvent composition, light, pressure, sound and magnetic fields, while the chemical or biochemical stimuli include pH, ions and specific molecular recognition events[15]. Smart hydrogels have been used in diverse applications, such as in making artificial muscles[7–11], chemical valves[12], immobilization of enzymes and cells[21], and concentrating dilute solutions in bioseparation[22–24]. Environment-sensitive hydrogels are ideal candidates for developing self-regulated drug delivery systems.

## 2. Classification of hydrogels

Hydrogels are broadly classified into two categories Permanent / chemical gel and Reversible / physical gel. Permanent / chemical gel, are called 'permanent' or 'chemical' gels when they are covalently cross-linked (replacing hydrogen bond by a stronger and stable covalent bonds) networks. They attain an equilibrium swelling state which depends on the polymer-water interaction parameter and the crosslink density[13-17].

Reversible / physical gel, are called 'reversible' or 'physical' gels when the networks are held together by molecular entanglements, and / or secondary forces including ionic, hydrogen bonding or hydrophobic interactions. In physically cross-linked gels, dissolution is prevented by physical interactions, which exist between different polymer chains. All of these interactions are reversible, and can be disrupted by changes in physical conditions or application of stress[8].

## 3. Environment sensitive hydrogels

There are several classes of environment sensitive hydrogel according the surrounding or stimuli to which they are exposed-

1) Temperature Sensitive (Thermosensitive) Hydrogel
2) pH Sensitive Hydrogel
3) Glucose Sensitive Hydrogel
4) Electric Signal Sensitive Hydrogel
5) Light Sensitive Hydrogel

## 4. Thermosensitive hydrogels

### 1) Polymer structures

Temperature-sensitive hydrogels are probably the most commonly studied class of environmentally sensitive polymer systems in drug delivery research[2]. Many polymers exhibit a temperature-responsive phase transition property. The structures of some of those polymers are shown in Figure 1.

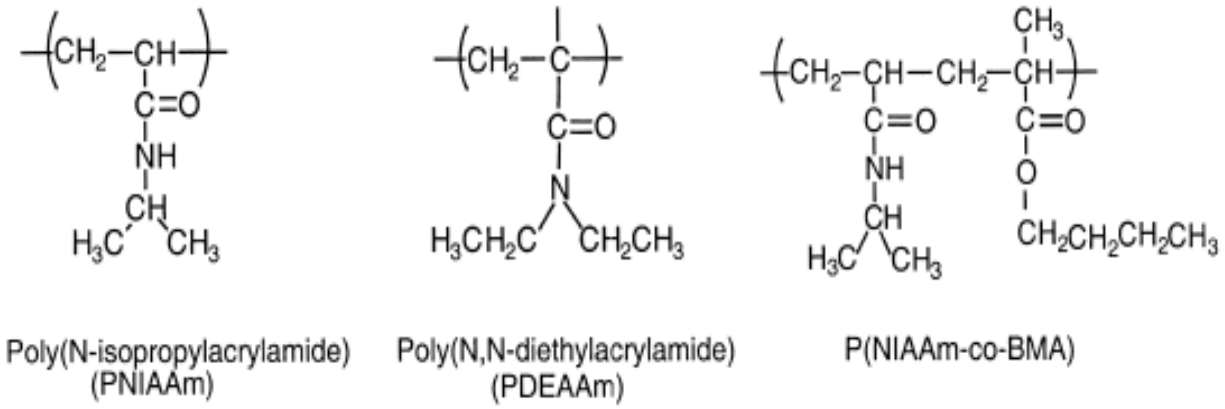


**Figure 1.** Structure of thermosensitive polymers

The common characteristic of temperature-sensitive polymers is the presence of hydrophobic groups, such as methyl, ethyl and propyl groups. Of the many temperature-sensitive polymers, poly (*N*-isopropylacrylamide) (PNIPAAm) is probably the most extensively used. Poly (*N*,*N*-diethylacrylamide (PDEAAm) is also widely used because of its lower critical solution temperature (LCST) in the range of 25–328C, close to the body temperature. Copolymers of NIPAAm can also be made using other monomers, e.g. butyl methacrylate (BMA), to alter the LCST. Certain types of block copolymers made of poly (ethylene oxide) (PEO) and poly (propylene oxide) (PPO) also possess an inverse temperature sensitive property. Because of their LCST at around the body temperature, they have been used widely in the development of controlled drug delivery systems based on the sol–gel phase conversion at the body temperature[26-28]. A large number of PEO–PPO block copolymers are commercially available under the names of PluronicsÒ (or PoloxamersÒ) and TetronicsÒ. Their structures are shown in Figure 2.

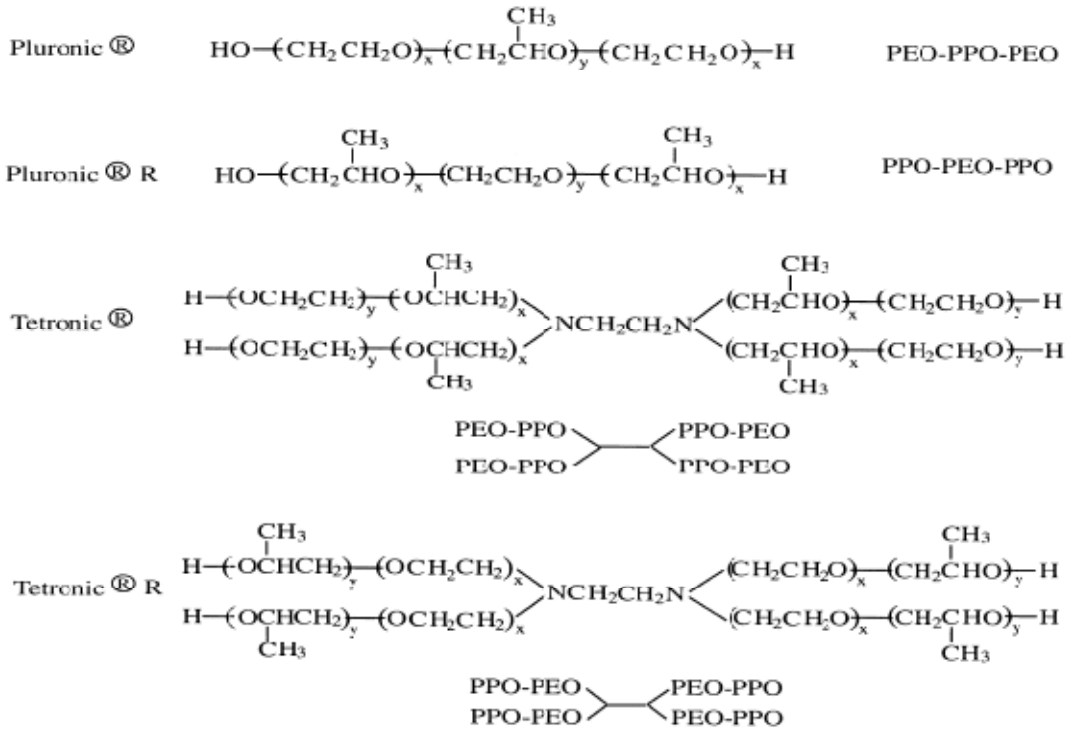


**Figure 2.** Polymer structures of PluronicÒ, PluronicÒ R, TetronicÒ and TetronicÒ R

## 2) Properties of thermosensitive hydrogels

Most polymers increase their water-solubility as the temperature increases. Polymers with LCST, however, decrease their water-solubility as the temperature increases. Hydrogels made of LCST polymers shrink as the temperature increases above the LCST. This type of swelling behavior is known as inverse (or negative) temperature-dependence. The inverse temperature-dependent hydrogels are made of polymer chains that either possess moderately hydrophobic groups (if too hydrophobic, the polymer chains would not dissolve in water at all) or contain a mixture of hydrophilic and hydrophobic segments. At lower temperatures, hydrogen bonding between hydrophilic segments of the polymer chain and water molecules are dominates, leading to enhanced dissolution in water. As the temperature increases, however, hydrophobic interactions among hydrophobic segments become strengthened, while hydrogen bonding becomes weaker. The net result is shrinking of the hydrogels due to inter-polymer chain association through hydrophobic interactions. In general, as the polymer chain contains more hydrophobic constituent, LCST becomes lower[19]. The LCST can be changed by adjusting the ratio of hydrophilic and hydrophobic make copolymers of hydrophobic (e.g. NIPAAm) and segment of the polymer. One way is to hydrophilic (e.g. acrylic acid) monomers[26]. The continuous phase transition of PNIPAAm is known to be changed to a discontinuous one by incorporating into the gel network[23, 24] or by changing solvent a small amount of ionizable group composition[15]. Copolymerization of NIPAAm with different types of monomers results in hydrogels with more versatile properties, such as faster rates of shrinking when heated through the LCST[26], and sensitivity to additional stimuli. If the polymer chains in hydrogels are not co may undergo sol–gel phase transitions, instead of valently crosslinked, temperature-sensitive hydrogels swelling–shrinking transitions. The thermally reversible gels with inverse temperature dependence become sol at higher temperatures. Polymers that show this type of behavior are block copolymers of PEO and PPO as shown in Figure 2. The hydrophobic PPO block can be replaced with other hydrophobic polymers. For example, PEO-containing block copolymers with poly (lactic acid) show the same thermoreversible behavior. In this case, the poly (lactic acid) segment provides a biodegradable property. Temperature-sensitive hydrogels can also be made using temperature-sensitive crosslinking agents. A hybrid hydrogel system was assembled from water soluble synthetic polymers and a well-defined protein-folding motif, the coiled coil[17]. The hydrogel underwent temperature-induced collapse due to the cooperative conformational transition. Using temperature-sensitive crosslinking agents adds a new dimension in designing temperature-sensitive hydrogels.

## 5. Methods of preparation of thermosensitive hydrogel

## 1) Physical cross-linking

There has been an increased interest in physical or reversible gels due to relative ease of production and the advantage of not using cross-linking agents. These agents affect the integrity of substances to be entrapped (e.g. cell, proteins, etc.) as well as the need for their removal before application. Careful selection of hydrocolloid type, concentration and pH can lead to the formation of a broad range of gel textures and is currently an area receiving considerable attention, particularly in the food industry [11].

### a) Heating/cooling a polymer solution

Physically cross-linked gels are formed when cooling hot solutions of gelatine or carrageenan. The gel formation is due to helix-formation, association of the helices, and forming junction zones. Carrageenan in hot solution above the melting transition temperature is present as random coil conformation. Upon cooling it transforms to rigid helical rods.

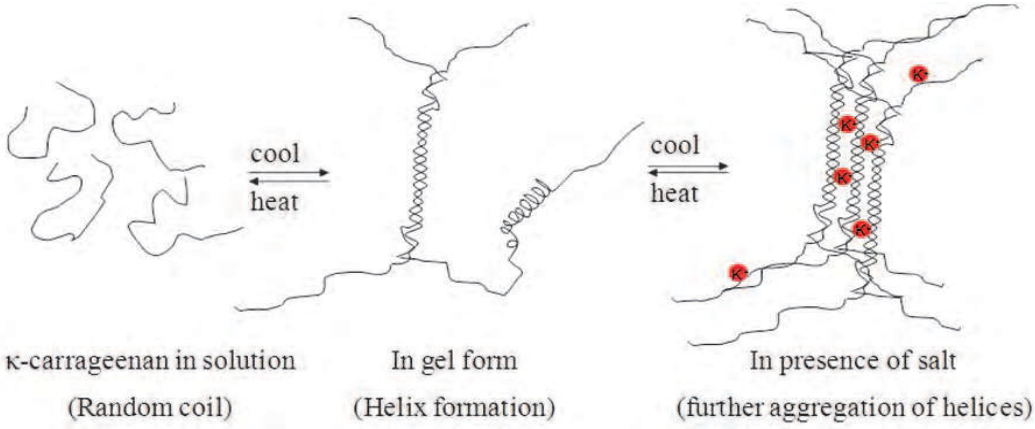


**Figure 3.** Gel formation due to aggregation of helix upon cooling a hot solution of carrageenan

In presence of salt ($K^+$, $Na^+$, etc.), due to screening of repulsion of sulphonic group (SO–3), double helices further aggregate to form stable gels (Figure 3). In some cases, hydrogel can also be obtained by simply warming the polymer solutions that causes the block copolymerisation. Some of the examples are polyethylene oxide-polypropylene oxide, polyethylene glycol-polylactic acid hydrogel[11-13].

Ionic polymers can be cross-linked by the addition of di- or tri-valent counterions. This method underlies the principle of gelling a polyelectrolyte solution (e.g. $Na^+$ alginate-) with a multivalent ion of opposite charges (e.g. $Ca^{2+}$ + $2Cl^-$) (Figure 4). Some other examples are chitosan-polylysine, chitosan-glycerol phosphate salt, chitosan-dextran hydrogels[20].

### b) Ionic interaction

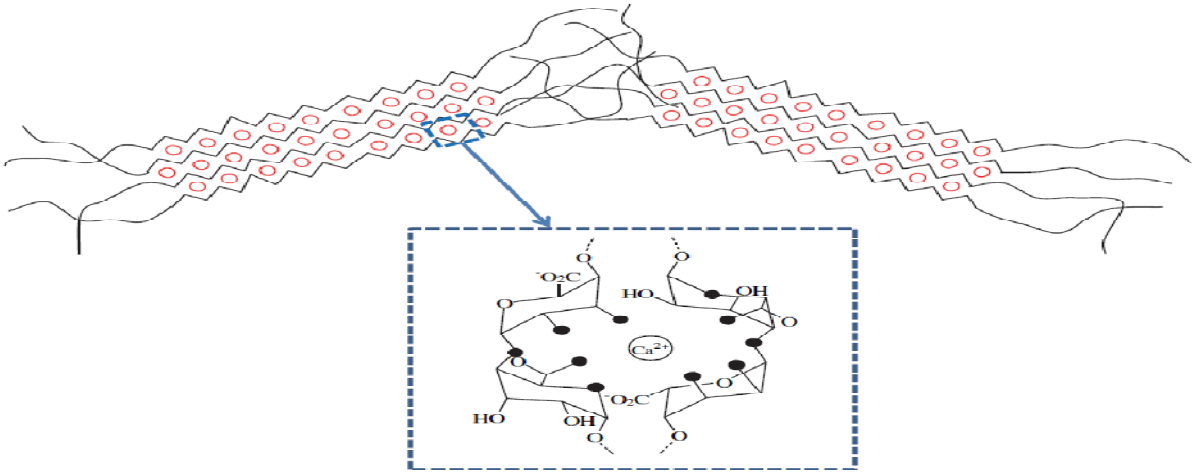


**Figure 4.** Ionotropic gelation by interaction between anionic groups on alginate ($COO^-$) with divalent metal ions ($Ca^{2+}$)

### c) Complex coacervation

Complex coacervate gels can be formed by mixing of a polyanion with a polycation. The underlying principle of this method is that polymers with opposite charges stick together and form soluble and insoluble complexes depending on the concentration and pH of the respective solutions (Figure 5). One such example is coacervating polyanionic xanthan with polycationic chitosan. Proteins below its isoelectric point are positively charged and likely to associate with anionic hydrocolloids and form polyion complex hydrogel (complex coacervate)[4-7].

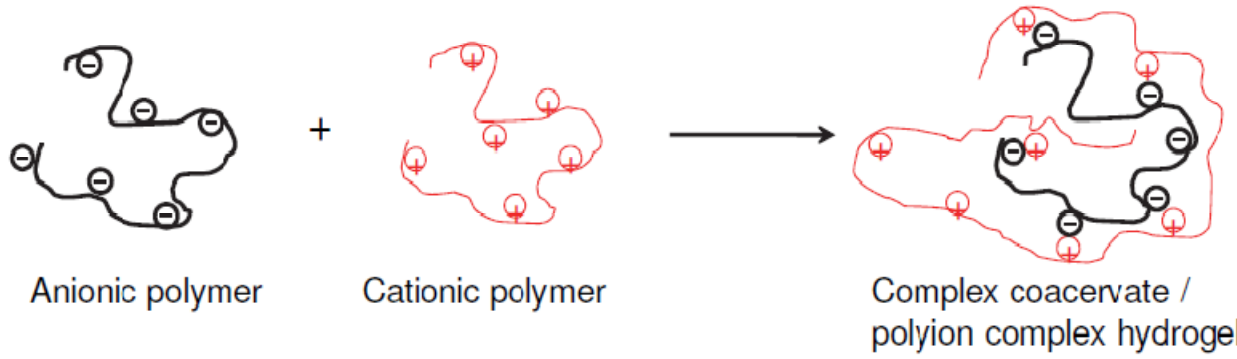


**Figure 5.** Complex coacervation between a polyanion and a polycation

### d) H-bonding

H-bonded hydrogel can be obtained by lowering the pH of aqueous solution of polymers carrying carboxyl groups. An example of such hydrogel is a hydrogen-bound CMC (carboxymethyl cellulose) network formed by dispersing CMC into 0.1M HCl[16].

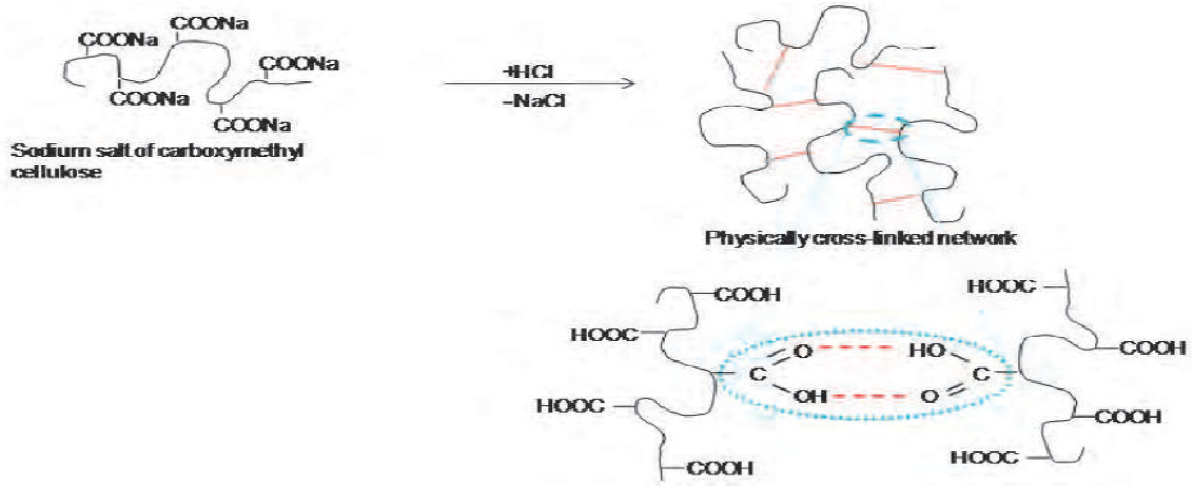


**Figure 6.** Hydrogel network formation due to intermolecular H-bonding in CMC at low pH

The mechanism involves replacing the sodium in CMC with hydrogen in the acid solution to promote hydrogen bonding (Figure 6). The hydrogen bonds induce a decrease of CMC solubility in water and result in the formation of an elastic hydrogel.

### e) Maturation (heat induced aggregation)

Gum arabic (Acacia gums) is predominately carbohydrate but contain 2-3% protein as an integral part of its structure. Three major fractions with different molecular weights and protein content have been identified following fractionation by hydrophobic interaction chromatography with different molecular weights and protein content. These are arabinogalactan protein (AGP), arabinogalactan (AG) and glycoprotein (GP). Aggregation of the proteinaceous components, induced by heat treatment, increases the molecular weight and subsequently produces a hydrogel form with enhanced mechanical properties and water binding capability. The molecular changes which accompany the maturation process demonstrate that a hydrogel can be produced with precisely structured molecular dimensions. The controlling feature is the agglomeration of the proteinaceous components within the molecularly disperse system that is present in of the naturally occurring gum[9].

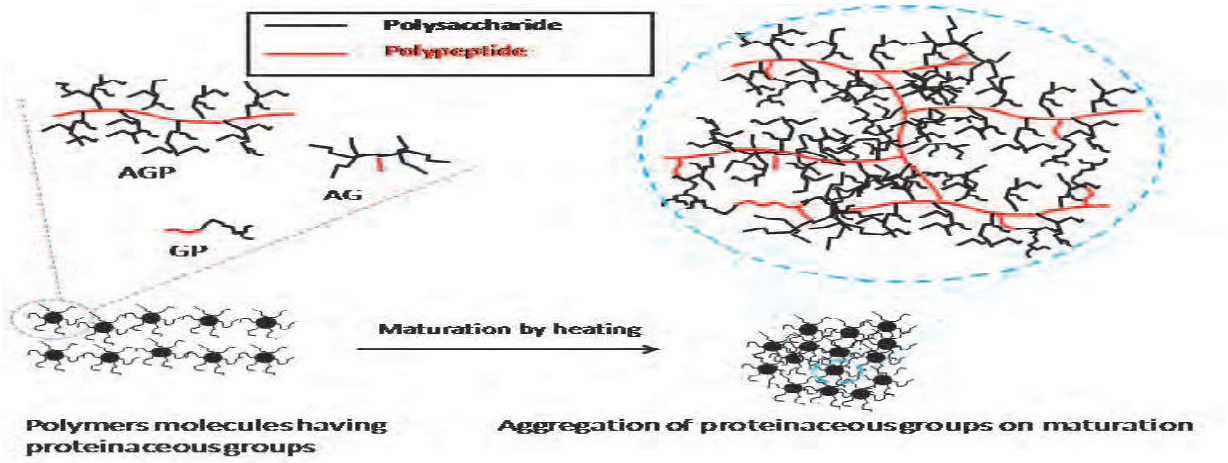


**Figure 7**. Maturation of gum arabic causing the aggregation of proteinaceous part of molecules leading to cross-linked hydrogel network

### f) Freeze thawing

Physical cross-linking of a polymer to form its hydrogel can also be achieved by using freeze-thaw cycles. The mechanism involves the formation of microcrystals in the structure due to freeze-thawing. Examples of this type of gelation are freeze-thawed gels of polyvinyl alcohol and xanthan[11].

## 2) Chemical cross-linking

Chemical cross-linking covered here involves grafting of monomers on the backbone of the polymers or the use of a cross-linking agent to link two polymer chains. The cross-linking of natural and synthetic polymers can be achieved through the reaction of their functional groups (such as OH, COOH, and NH2) with cross-linkers such as aldehyde (e.g. glutaraldehyde, adipic acid dihydrazide). There are a number of methods reported in literature to obtain chemically cross-linked permanent hydrogels. Among other chemical cross-linking methods, and hydrophobic interactions, (incorporating a polar hydrophilic group by hydrolysis or oxidation followed by covalent cross-linking) are also used to obtain chemically cross-linked permanent hydrogels. The following section reviews the major chemical methods (i.e. crosslinker, grafting, and radiation in solid and/or aqueous state) used to produce hydrogels from a range of natural polymers[10].

### a) Chemical cross-linkers

Cross-linkers such as glutaraldehyde, epichlorohydrin, etc have been widely used to obtain the cross-linked hydrogel network of various synthetic and natural polymers. The technique mainly involves the introduction of new molecules between the polymeric chains to produce cross-linked chains (Figure 8). One such example is hydrogel prepared by cross-linking of corn starch and polyvinyl alcohol using glutaraldehyde as a cross-linker. The prepared hydrogel membrane could be used as artificial skin and at the same time various nutrients/healing factors and medicaments can be delivered to the site of action.CMC chains can also be cross-linked by incorporating 1, 3-diaminopropane to produce CMC-hydrogel suitable for drug delivery through the pores[10].

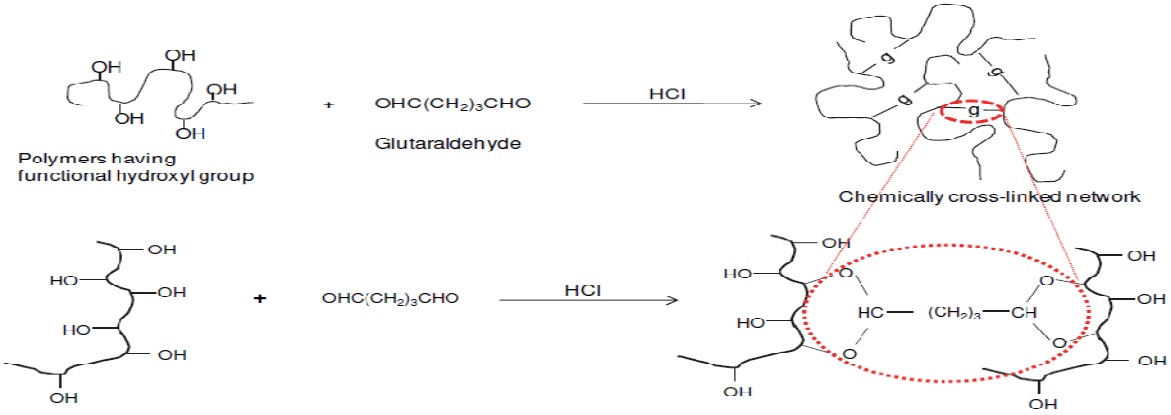


**Figure 8.** Schematic illustration of using chemical cross-linker to obtain cross-linked hydrogel network

### b) Grafting

Grafting involves the polymerisation of a monomer on the backbone of a preformed polymer. The polymer chains are activated by the action of chemical reagents, or high energy radiation treatment. The growth of functional monomers on activated macroradicals leads to branching and further to cross-linking (Figure 9)[10].

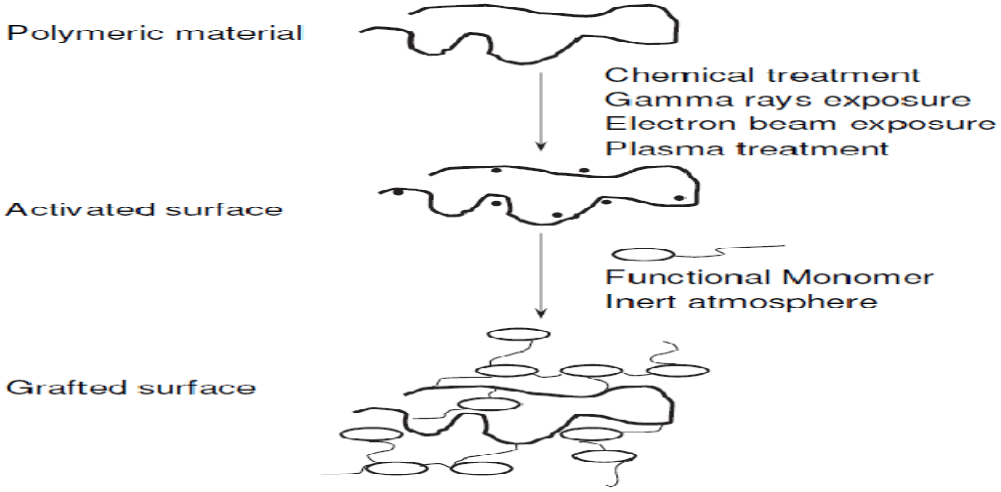


**Figure 9.** Grafting of a monomer on preformed polymeric backbone leading to infinite branching and cross-linking

### c) Radiation cross-linking

Radiation cross-linking is widely used technique since it does not involve the use of chemical additives and therefore retaining the biocompatibility of the biopolymer. Also, the modification and sterilization can be achieved in single step and hence it is a cost effective process to modify biopolymers having their end-use specifically in biomedical application. The technique mainly relies on producing free radicals in the polymer following the exposure to the high energy source such as gamma ray, x-ray or electron beam. The action of radiation (direct or indirect) will depend on the polymer environment (i.e. dilute solution, concentrated solution, solid state)[10].

## 6. Characterization of thermosensitive hydrogel

### 1) pH

pH can be determined by using digital pH meter[3].

### 2) Clarity

The clarity is determined by visual inspection against white background[3].

### 3) Homogeneity

Homogeneity is determined by visual inspection after the gels have been set in the container[3].

### 4) Gelation temperature

2 ml aliquot of gel is transferred to test tube. Test tubes are immersed in a water bath. The temperature of water bath is increased slowly and left to equilibrate for 5 min at each new setting. The sample is then examined for gelation, which is said to have occurred when the meniscus should no longer move upon tilting the test tube to 90°[25].

### 5) Viscosity

Viscosity of formulation can be checked by Brookfield viscometer (Capcalc V2.2) using model 1x with cone number 01, at an angular velocity of 5 RPM and shear rate of 66.66 for time interval of 10 sec. at respective gelation temperature for formulation[23].

### 6) Gel strength

A sample of 5 gm of formulation is gelled at 37°C. A weight of 3.5 gm is placed on the gel surface. The gel strength is then determined by the time in seconds required by the weight to penetrate 0.5 cm in the gel. The gel strength is then reported[5].

### 7) Spreadability

Spreadability can be determined by wooden block and glass slide apparatus. Weights about 20 gm are added to the pan and the time can be noted for upper slide (movable) to separate completely from the fixed slide. The normal range of spreadability is 5-7 gm.cm/sec[5].

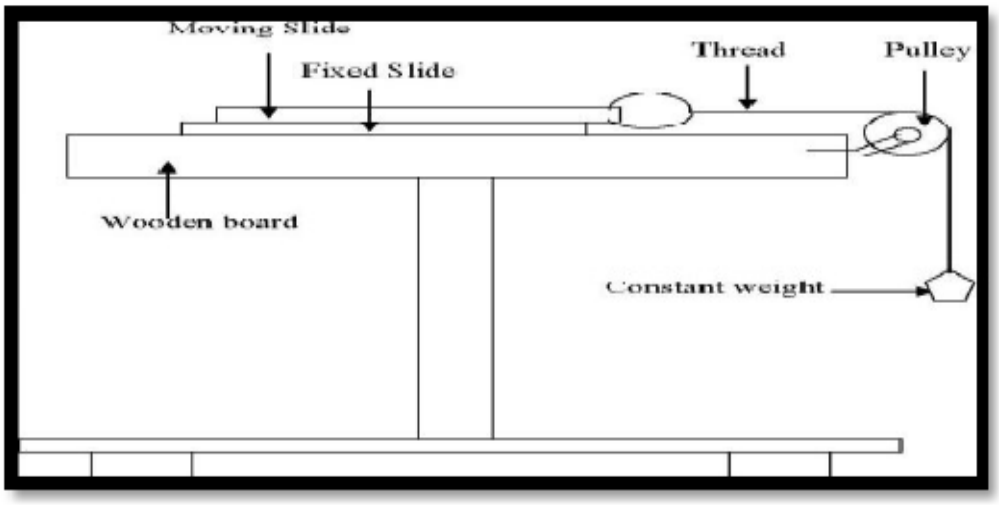


**Figure 10.** Schematic representation of apparatus for determination of spreadability of gel

Spreadability is can be calculated by using the formula:

$$S = ML/T$$

Where,
S = Spreadability (gm.cm/sec.).
M = Weight tied to upper slide.
L = Length of the glass slide.
T = Time taken to separate the slide completely from each other.

### 8) Bioadhesive strength

Bioadhesive strength can be determined by measuring the force required to detach the formulation from cellophane membrane by using wooden block and glass slide apparatus. 1 gm of gel is taken on glass slide wrapped with cellophane membrane. The movable glass slide is placed on fixed slide and intimate contact is provided. Two minute contact time is given to ensure intimate contact between membrane and formulation. The weight is added in the pan until slides get detached[25]. The bioadhesive force, expressed as the detachment stress in dyne/cm$^2$ is determined by the formula:

$$\text{Detachment stress} = m \cdot g/A$$

Where,
m = Weight required to detach two glass slides from each other (gm).
g = Acceleration due to gravity (980 cm/s$^2$).
A = Area of membrane exposed (cm$^2$).

### 9) PPL (Plane Polarized Light) imaging

Investigation of the gels for the presence of liquid crystals can be done by examination under polarized light microscope (Lawrence and Mayo, London) equipped with cross polarizer and attached to digital Nikon Coolpix P6000 camera and monitor. A small quantity of the sample is placed on a clean glass slide. The existence of birefringence is verified by observation under crossed polar employing magnification of 20X and 40X. Photomicromicrographs of these samples are taken[16].

### 10) Drug content

A specific quantity (100 mg) of developed gel is taken separately and 100 mg of gel is dissolved in 100 ml phosphate buffer solution having pH 7.4. The volumetric flasks containing gel solutions are shaken for 2 hrs. by using mechanical shaker in order to get complete solubility of drug. Solution is filtered and estimated spectrophotometrically using phosphate buffer solution of pH 7.4 as blank[5].

## 7. Applications of thermosensitive hydrogels

### 1) Applications of hydrogels in drug delivery

Hydrogels have been used for the development of controlled delivery systems for a long time. When the drug bearing hydrogel comes in contact with aqueous medium, water penetrates into the system and dissolves the drug. Diffusion is the main phenomena by which the dissolved drug diffuses out of the delivery systems to the surrounding aqueous medium. Diffusion is defined as the movement of the individual molecules from the region of high solute concentration to a region of low concentration when the systems are separated by a polymeric membrane. This phenomenon of diffusion is mainly attributed to the Brownian motion. The delivery systems employing hydrogels for controlled release can be categorized into reservoir and matrix devices. As mentioned earlier, hydrogels are 3-dimensionally cross-linked polymer networks and hence act as a permeable matrix/membrane for the drug thereby governing the release rate of the drug. The diffusion of the drug through the hydrogels may be affected by the property (viz. pH sensitivity, light sensitivity, pressure sensitivity) of the hydrogel depending on the chemistry of the hydrogels and has been used successfully to design delivery systems which may release drug at a suitable environment[11].

## 2) Applications of hydrogels in tissue engineering

Tissue engineering (TE) is a multidisciplinary approach and involves the expertise of materials science, medical science and biological science for the development of biological substitutes (tissue/organ). It is emerging as an important field in regenerative medicine. It has got three basic components namely, cells/tissues, scaffolds and implantation and/or grafting. The principles of TE have been used extensively to restore the function of a traumatized/malfunctioning tissues or organs. In practice, the patient's cells are generally combined with a scaffold for generating new tissue. A scaffold can be made up of either ceramic or polymer, which can be either permanent or resorbable. The pore size of the scaffolds should be >80 μm. This is necessary for the cell migration into the core of the scaffolds, angiogenesis, and supply of nutrients to the cells and to take away the metabolic products away from the cells. The scaffolds made up of polymers are generally hydrogels. Every year thousands of people are victims of tissue loss and organ failure caused either due to disease or trauma. Also, there is a shortage of organ donors because of the religious beliefs and/or medical complications. Keeping the above facts in mind, TE can be a useful tool to replace the damaged/malfunctioning organs or tissues. Recently the use of resorbable hydrogels in TE has gained much importance because (a) it is easy to process the polymers; (b) the properties of the hydrogels can be tailored very easily; and (c) resorbable polymers like polylactic acid (PLA), polyglycolic acid (PGA), and their co-polymers (PLA-co-PGA; PLGA) are being used for biomedical application since long time[25].

## 3) Applications of hydrogels in wound healing

The use of hydrogels in the healing of wounds dates back to late seventies or early eighties. As mentioned earlier, hydrogel is a crosslinked polymer matrix which has the ability to absorb and hold water in its network structure. Hydrogels act as a moist wound dressing material and have the ability to absorb and retain the wound exudates along with the foreign bodies, such as bacteria, within its network structure. In addition to this, hydrogels have been found to promote fibroblast proliferation by reducing the fluid loss from the wound surface and protect the wound from external novae necessary for rapid wound healing. Hydrogels help in maintaining a micro-climate for biosynthetic reactions on the wound surface necessary for cellular activities. Fibroblast proliferation is necessary for complete epithelialisation of the wound, which starts from the edge of the wound. Since hydrogels help to keep the wound moist, keratinocytes can migrate on the surface. Hydrogels may be transparent, depending on the nature of the polymers, and provide cushioning and cooling/ soothing effects to the wound surface. The main advantage of the transparent hydrogels includes monitoring of the wound healing without removing the wound dressing. The process of angiogenesis can be initiated by using semi-occlusive hydrogel dressings, which is initiated due to temporary hypoxia. Angiogenesis of the wound ensures the growth of granulation tissue by maintaining adequate supply of oxygen and nutrients to the wound surface. Hydrogel sheets are generally applied over the wound surface with backing of fabric or polymer film and are secured at the wound surface with adhesives or with bandages[18].

## 4) Application of hydrogels for gene delivery

Gene delivery is defined as the incorporation of foreign DNA particles into the host cells and can be mediated by viral and non-viral methods. The delivery of gene into the host cells by utilizing a virus uses the capability of a virus to incorporate its DNA into the host cells. For the purpose retroviruses and adenoviruses have been used. These viral vectors are used as they can provide efficient transduction and high gene expression. At the same time, the use of viral vectors is quite limited as they can produce immunogenic reactions or mutagenesis of transfected cells. Hence, scientists are tuning their interest towards the available non-viral techniques, which produces less complexity. The non-viral techniques include the use of a gene gun, electroporation and sonication. Of late researchers have started the use of polymers, viz. poly-L-lysine (PLL), polyamidoamine dendrimer (PAMAM), polyethylenimmine (PEI), PGA, PLA and PLGA, for gene delivery. Though PAMAM and PEI can provide high transfection efficiency, their use is limited due to their poor degradability. This is why the use of biodegradable polymers, viz. PLA, PLGA and PGA, has gained importance. The use of PEG-PLGA-PEG hydrogel for the delivery of plasmid-beta 1 gene increased the wound healing process in diabetic mouse model[3].

## 8. Conclusion

Environmentally-sensitive hydrogels have enormous potential in various applications. Some environmental variables, such as low pH and elevated temperatures, are found in the body. For this reason, either pH-sensitive and/or temperature sensitive hydrogels can be used for site-specific controlled drug delivery. Hydrogels that are responsive to specific molecules, such as glucose or antigens, can be used as biosensors as well as drug delivery systems. Light-sensitive, pressure-responsive and electro-sensitive hydrogels also have potential to be used in drug delivery and bioseparation.

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