Recent Advances in Thermosensitive Hydrogels as Drug Delivery Systems: A Review

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Abstract: Polymers that exhibit physicochemical responses to stimuli have been widely explored as potential drug delivery systems. Different kind of stimuli investigated to date includes, for example, chemical substances and changes in temperature, pH and electric fields. Polymers that exhibit dramatic changes in their behavior in an aqueous solution at temperatures close to the body temperature are of particular interest in drug delivery and biomedical applications. Thermosensitive polymers have a wide range of applications, specially, the thermosensitive triblock copolymers because they exhibit unique aqueous solution properties, biodegradability and biocompatibility. These copolymers can be designed to be used as potential drug delivery systems for therapeutic protein drugs or poorly water soluble drugs. This article reviews the applications of polymer solutions with the ability to form *in situ* implants under temperature changes, in areas of interest to biomedical, pharmacist and engineer scientists. Recent advantages on thermosensitive and biodegradable polymers are discussed to give a wide overview of the available strategies to modify them in order to make them suitable for potential applications in health products.

Keywords: Drug delivery, gelation temperature, *in situ* forming gel, thermosensitive, triblock copolymers.

1. INTRODUCTION

In recent years, drug delivery systems employing polymers have become an extensively studied area in pharmaceutical technology. Certain polymer properties can be modified to enable fulfilling specific criteria to design suitable drug delivery systems for biomedical applications. The challenge to create unique functional polymeric systems mimicking natural systems is claimed to be the driving force towards a new generation of polymers, named stimuli-sensitive or smart polymers, which change their structures and functions in response to environmental stimuli. This technology makes possible the application of pharmaceutical formulations in the liquid state and subsequent *in situ* gelification providing a prolonged release of the therapeutic drug at the application site. In addition to the success of controlled drug release systems in pharmaceutical and biopharmaceutical fields, pioneering research is finding increasing applications in medical and biotechnological fields [1]. Another interesting alternative to obtain stimuli-responsive polymers is the molecular imprinting technique for introducing regions with a highly specific molecular arrangement into a polymeric matrix. This technique has also been used in biological applications such as drug delivery systems, and they have also been successfully applied as excipients in controlled delivery systems [2].

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In order just to show a barometer on the interest of thermosensitive polymers, Fig. (**1**) shows the collected outcome data obtained by invoking the keywords "thermosensitive" and "polymer" from three well-known scientific publication databases in the last 20 years. The number of records displayed by the year of publishing evidences an increasing interest and research activity in the last decade, i.e., once the proof of concept and technology development were convincing enough to the academic and business communities.

Hydrogels have been object of extensive research in recent decades since their properties, such as high water content and the possible control on the kinetics of swelling, make them very attractive for R&D in pharmaceutical technology. These systems are liquids that can be introduced into the body with a minimally invasive technique before solidifying or gelling in the target tissue, organ or body cavity. Polymer matrices of *in situ* forming gel provide several advantages over other systems that require implantation surgery procedures and sometimes must even be withdrawn. Moreover, if necessary, several therapeutic agents can be incorporated in these polymers by simple mixing. Hydrogels are presently under investigation as matrices for the controlled release of bioactive molecules, in particular pharmaceutical proteins, and for the encapsulation of living cells. However, for these applications it is often required that the gels degrade under physiological conditions and possess good mechanical resistance. Hydrogels can be classified into different groups, just for convenience, based on the source of origin, chemical structure, preparation method, electric charge, physical structure, crosslinking, or function. There

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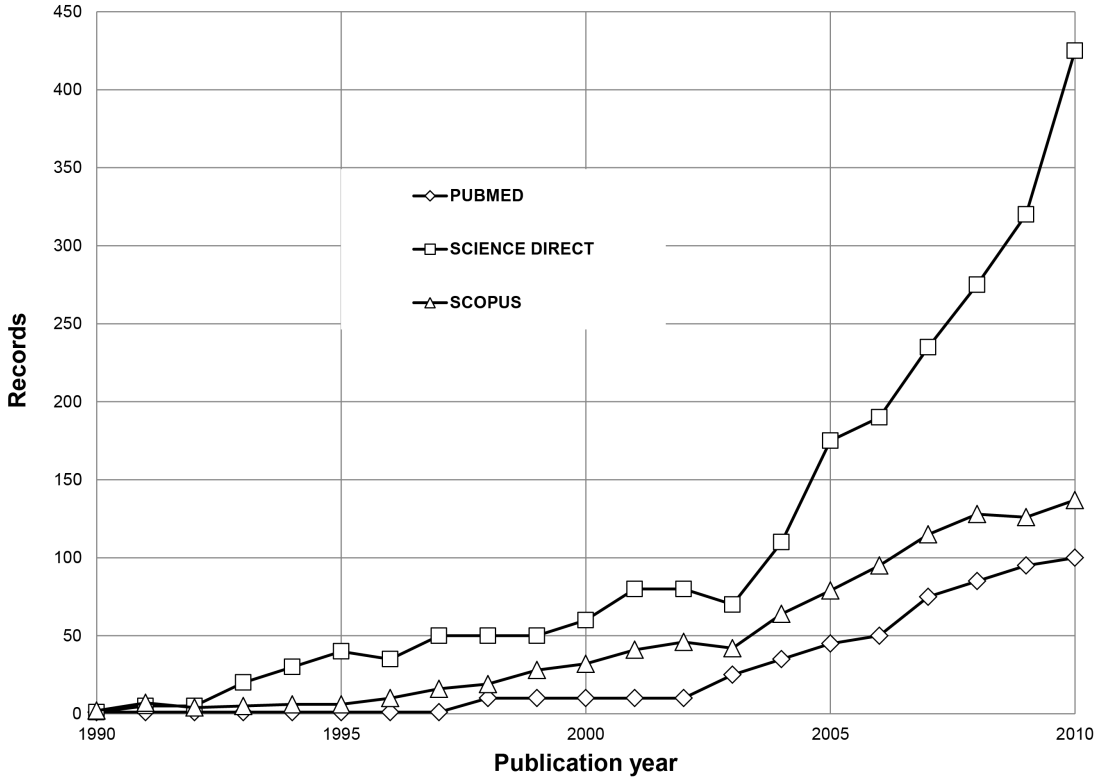


Fig. (1). Number of papers containing the keywords "thermosensitive" and "polymer" in the last 20 years.

are two types of crosslinking: chemical and physical crosslinking. In the chemical crosslinking, all polymer chains are crosslinked to each other by covalent bonds, and thus, strictly speaking, each hydrogel is one molecule. For this reason, a hydrogel is sometimes called a ‘‘supermacromolecule.’’ While chemical crosslinking is well defined by each chemical bond, physical crosslinking is made through multiple, simultaneous interactions of weaker bonding, such as hydrogen bonding and hydrophobic interactions. The area of such physical bonding among laterally associated polymer chains is known as a junction zone [3]. Censi *et al.* [4] evaluated the correlation between polymer architecture and the hydrogel properties, particularly rheological, swelling, degradation properties and release behavior. For this purpose, photopolymerized thermosensitive A-B-A triblock copolymer hydrogels composed of poly(N-(2-hydroxypropyl) methacrylamide lactate) A-blocks, partly derivatized with methacrylate groups to different extents (10, 20, and 30%) and hydrophilic poly(ethylene glycol) B-blocks of different molecular weights (4, 10, and 20 kDa) were synthesized. The authors concluded that because the mechanical properties, degradation, and release profiles can be fully controlled by polymer design and concentration, these hydrogels are suitable for controlled protein release.

In this overview, different chemical and physical crosslinking methods used for the design of biodegradable hydrogels to improve the physicochemical properties were summarized and discussed by Hennink *et al.* [5]. The authors reported that chemical crosslinking is a highly versatile method to create hydrogels with good mechanical stability. However, the crosslinking agents used are often toxic compounds, so they have to be extracted from the gels before they can be applied. Moreover, crosslinking agents can give unwanted reactions with the bioactive substances present in the hydrogel matrix. Such adverse effects are avoided with the use of physically crosslinked gels.

Temperature-sensitive hydrogels are probably the most common studied class of environment-sensitive polymer systems in drug delivery research. These hydrogels are able to swell or deswell as a result of a change in the temperature of the surrounding fluid. For convenience, temperature-sensitive hydrogels are classified into negative thermosensitive and positive thermosensitive gels [6].

1.1. Negative Thermosensitive Hydrogels

Negative temperature-sensitive hydrogels have a lower critical solution temperature (LCST), which may be defined as the critical temperature below which the polymer swells in the solution, while above it the polymer contracts. Below the LCST, the enthalpy term, related to the hydrogen bonding between the polymer and the water molecules, is responsible for the polymer swelling. When the temperature is raised above the LCST, the entropy term (hydrophobic interactions) dominates, leading to polymer contraction. This behavior is also known as reverse thermal gelation and represents one of the most promising strategies in the development of biomaterials.

The efficiency of the hydrogen bonding process has negative temperature dependence; above the LCST the hydrogen bonds between the monomer side groups and water molecules will be increasingly disrupted with increasing temperature [7].

The backbones of the polymer, long chains of C–C bonds to which the side chains are attached, are hydrophobic and tend to reduce their surface area exposed to the highly polar water molecules. Normally, when hydrogen bonds between the side groups and the water are present, the aggregation of the backbone is prevented because the hydrogen bond interactions with the water molecules are stronger than the backbone interactions. When the temperature increases, hydrogen bonds are broken by thermal agitation, then aggregation takes place, resulting in shrinkage of the thermosensitive hydrogel when the LCST value is reached. A well-known polymer with LCST at 32°C is poly(N-isopropyl acrylamide) (pNIPAAm) which has been extensively employed as a negative thermosensitive hydrogel. These hydrogels show an on–off drug release with "ON" at a low temperature and "OFF" at a high temperature allowing the desired drug release.

It is a common strategy to modulate the LCST of a polymer by incorporating hydrophilic or hydrophobic moieties in the polymer structure. For example, when pNIPAAm is copolymerized with 18% of the hydrophilic monomer acrylamide (AAm), the LCST increases up to about 45°C, whereas the LCST decreases to about 10°C when 40% of the hydrophobic monomer N-tert-butyl acrylamide (N-tBAAm) is added [8]. Other polymers belonging to the pNIPAAm family are poly(N,N′-diethyl acrylamide) with LCST values around 26-35°C [9].

1.2. Positive Thermosensitive Hydrogels

A positive temperature-sensitive hydrogel has an upper critical solution temperature (UCST). The hydrogel contracts upon cooling below the UCST. Polymer networks of poly(acrylic acid) (pAA) and polyacrylamide (pAAm) or poly(acrylamide-co-butyl methacrylate) exhibit a positive temperature dependence of swelling [10]. Most commonly used thermoreversible gels are prepared from poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide) known also as Pluronic® or Poloxamers. The polymer solution is a free-flowing liquid at room temperature but gels at body temperature. Such a system would be easy to administer into a desired body cavity. In some cases, if lowering the amount of thermogelling polymer is necessary, it may be blended with a pH-sensitive, reversibly gelling polymer. Recently, new series of biodegradable triblock copolymers were designed. Polymers, consisting of poly(ethylene glycol)–poly-(d,l-lactic acid-co-glycolic acid)–poly(ethylene glycol) (PEG–PLGA–PEG) [11] or PLGA–PEG–PLGA [12], were investigated for sustained injectable drug delivery systems. Some natural polymers such as xyloglucan may also form thermoreversible gels [13].

Macromolecular therapeutic drugs require the use of polymeric systems, since these agents have very short half-life in blood plasma and are sensitive to physical or chemical degradation. Although many therapeutic proteins, peptides and DNA-based drugs are available due to advances in biotechnology, conventional routes of administration of these drugs require frequent doses to achieve a desirable therapeutic concentration in blood that can lead to poor patient compliance as well as undesirable side effects.

For these reasons, significant research efforts were performed to develop polymeric platforms for sustained and controlled release of proteinic drugs in order to reduce administration frequency. This interest has been driven by the advantages that these delivery systems possess, such as application simplicity, localized distribution for a site-specific action [14], prolonged administration periods and lower required drug dose in the body with the simultaneous reduction of unwanted side effects common to most of the forms of systemic administration, so improving the patient compliance. Furthermore, it offers the possibility of extending the validity of drug patents close to expire.

An interesting chronotherapeutic approach to design a thermoresponsive membrane for transdermal drug delivery was made by Lin (2004) [15]. In this work it is described the development of a thermo-responsive membrane by entrapping a single or binary liquid crystal to achieve an on-off switching drug delivery for transdermal application via the externally repeated cycle of temperature change, which may simulate the dosing time of therapeutic needs for human body.

Viscoelastic gels, with micro- and macroscopic properties conveniently designed to ensure long periods of residence and drug release, appear as potential starting systems. Thus, a polymer solution, capable to form *in situ* a suitable gel at a temperature close to physiological temperature, could be attractive for the development of drug release systems.

An ideal thermosensitive system could be imagined as a solution with flowing properties similar to those of a liquid at room temperature. However, the system must gel at body temperature with minimal syneresis. On the other hand, the drug load should be achieved by simple mixing. So, when administered intraocularly or parenterally, these ideal systems should exhibit a pH close to neutrality and should be bioresorbable. Such formulations, with controlled drug release, would avoid frequent administration of single drug doses as well as painful surgical procedures to insert solid implants. In order to obtain products approved by regulatory authorities, the excipients must comply with the requirements of safety, tolerability, biodegradability and sterilization. Furthermore, in parenteral administration situations, sustained release formulations should exhibit low viscosity to avoid painful injections. In actual facts, injectable *in situ* forming gels systems for intramuscular use have been recently developed for the production of drug controlled release and represent an attractive alternative for implant replacement, temporary prosthesis or preformed platform drug delivery.

This article reviews the applications of polymer solutions with the potential to form *in situ* implants under temperature changes, in areas of interest to biomedical, pharmacist and engineer scientists. It is mainly focused on the use of thermosensitive gels based on polymers such as N-isopropylacrylamide polymers (pNiPAAm) and poly (ethylene oxide)$_x$-poly (propylene oxide)$_y$-poly (ethylene oxide)$_x$(POE-POP-POE) and their respective copolymers, as well as biodegradable polyester copolymers poly (ethylene glycol) (PEG), copolymers of poly (ethylene oxide/D, L-lactic acid-co-glycolic acid) (PEO/PLGA), natural poly-

mers and derivatives, among other thermosensitive polymers that will be also studied.

2. NATURAL POLYMERS AND DERIVATIVES

2.1. Polysaccharides

2.1.1. Cellulose Derivatives

Cellulose is an unbranched polysaccharide polymer consisting of 1,4-β-linked glucopyranose units Fig. (**2A**). It is the chief constituent of fibrous plant material. Most aqueous solutions of natural polymers form a gel phase when temperature decreases. Classic examples of natural polymers that exhibit a sol-gel transition are gelatin and carrageenan. At elevated temperatures, these polymers adopt a random conformation in solution. When cooled, a continuous network is formed by the partial formation of a helix [16]. Some cellulose derivatives are an exception to this gelation mechanism. At low concentrations (1-10 wt %) their aqueous solutions are stable at low temperature, but gelling starts with heating. Methylcellulose (MC) Fig. (**2B**) and hydroxypropylmethylcellulose (HPMC) Fig. (**2C**) are typical examples of such polymer behavior. MC solutions form opaque gels between 40 and 50°C, while HPMC shows the phase transition between 75 and 90°C. These phase transition temperatures can be reduced by introducing chemical or physical modifications. For example, NaCl decreases the transition temperature of MC solutions down to 32-34°C. Similarly, through the reduction of hydroxypropyl molar substitution of HPMC, the transition temperature can be lowered up to around 40°C [17,18]. Gelation of MC or HPMC solutions is mainly caused by the hydrophobic interaction between molecules that contain methoxy substitution. At low temperatures, macromolecules are hydrated, and there are few polymer-polymer interactions. As the temperature rises, the polymers gradually loose hydration water, which is reflected in a relative viscosity decrease. Finally, when an enough, but not yet complete, polymer dehydration is produced, polymer-polymer associations take place and the system approaches to an infinite network structure, as reflected experimentally by a strong increase on relative viscosity [17,18]. This sol-gel transition phenomenon has been used to the design of *in situ* gelation systems. MC hydrogels provide a backbone to link specific biological moieties to control cellular adhesion, migration and infiltration [19]. MC forms hydrogel systems in which the mechanical properties can be regulated to a range of rigidities by modifying the solution concentration, ionic strength and/or molecular weight. Moreover, the thermoresponsive property of MC is appealing for neural tissue-engineering applications, particularly for situations where the implanted material needs to be used for irregularly shaped lesions/defects (e.g. spinal cord and traumatic brain injuries) [20,21]. Previously, Tate *et al.* [22] evaluated MC-based constructions with potential applications in tissue engineering (scaffolds) to repair brain defects. These systems exhibit low viscosity at 23°C and form intracerebral soft gels at 37°C. Gels were proven to be biocompatible, both in presence of culture cells and injured rat brain. More recently, Jin and Kim [23] reported the development of an injectable thermosensitive gel formed in aqueous solution by preparing complex coacervate composed of two oppositely charged biomacromolecules, the negatively charged chondroitin 6-sulfate and the positively charged high molecular weight gelatin type A, and co-formulating with MC. The combination of the complex coacervation with a thermoreversible gel demonstrated synergistic effects on the complex coacervate formation, the release rate of model proteins and the *in situ* gel depot formation. These systems showed sustained release patterns of the protein over 25 days with minimal initial bursts. Finally, Lina *et al.* [24] reported the *in vitro* evaluation of lysozyme-loaded microspheres in thermosensitive MC-based hydrogel. Their results indicated that the burst effect was avoided due to strengthening of the diffusion resistance in the gel. The formulation was able to deliver lysozyme for over 30 days at a rate of 32.8~g.d^{-1} following a nearly zero-order release profile, which exhibits its remarkable potential for effective application in long-term drug delivery.

2.1.2. Chitosan

Chitosan is a polysaccharide composed of polymers of glucosamine and N-acetylglucosamine produced by partial deacetylation of chitin Fig. (**2D**). It is commercially manufactured by chemical treatment of crustacean shells. It is a cationic, pH-dependent, biocompatible polymer soluble in water up to pH 6.2. Chitosan is currently receiving a great deal of interest for medical and pharmaceutical applications due to its low toxicity, good biocompatibility and biodegradability [25]. Thermosensitive solutions and hydrogels based on combinations of chitosan and disodium glycerophosphate salt have been developed for potential biomedical applications [26]. In the past few years, thermosensitive membranes consisting of chitosan and poly(lactide-co-glycolide) (PLGA) and other poly(α-hydroxy acid)s, such as poly(lactide) (PLA) or poly(glycolide) (PGA), have been used as carriers for controlled delivery of a wide range of bioactive agents, such as hormones, steroids, antibiotics and anti-cancer agents [27-29].

Ganji and Abdekhodaie [30] reported the obtention of a thermosensitive copolymer that was synthesized by graft copolymerization of PLGA copolymers onto the surface of chitosan membranes. These membranes exhibited a reversible swelling–shrinking behavior; and higher swelling ratios were observed at higher temperatures. Drug permeation studies were carried out using vancomycin hydrochloride and betamethasone sodium phosphate as model drugs. The authors concluded that these thermosensitive chitosan–g-PLGA membranes might be used to develop an intelligent drug delivery system due to the high biocompatibility of chitosan and PLGA. The stability of the chitosan solution at room temperature and gelation time increased as the degree of deacetylation of chitosan decreased [31]. As in other systems of polysaccharides, gels can be obtained with low concentrations of polymers (2 wt %).

Nazar *et al.* [32] have developed a thermosensitive drug delivery vehicle for nasal administration using N-trimethyl chitosan chloride, synthesized from chitosans of three different average molecular weights, combined with poly(ethylene glycol) and glycerophosphate. Rheological evaluations showed that these hydrogels exhibited relatively short sol-gel transition times at physiologically relevant temperatures. The sol-gel transition occurs at 32.5°C within 7 min.

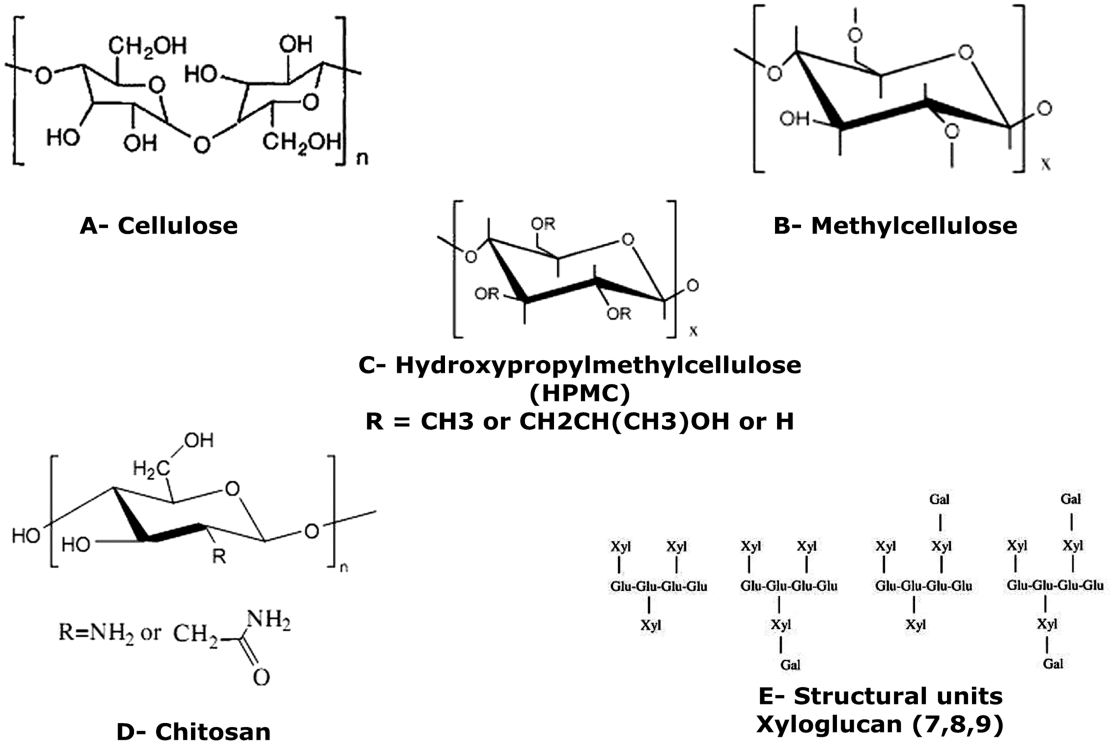


Fig. (2). Some chemical structures of the units of thermosensitive natural/semi-natural polymers.

On the other hand, injectable thermosensitive chitosan hydrogels were prepared by Schuetz *et al.* [33] for use in drug delivery systems and tissue engineering. Several phosphate-free polyols or polyoses were added as gelling agents to chitosan from two different sources. The authors obtained a formulation reconstituted from a lyophilizate displaying thermosensitive properties and still injectable. More recently, Li *et al.* [34] performed a study of the gel-sol-gel behavior of chitosan–inorganic phosphate solutions. According to the result of the rheological study, there are two phase transition points as a function of the temperature, corresponding to 30°C and 43°C.

Another interesting approach was conducted by Fang *et al.* [35]. The authors have developed thermosensitive hydrogels composed of pNIPAAm with chitosan (CPN) and chitosan + hyaluronic acid (CPNHA) using nalbuphine as drug model. A slight difference in the transition temperatures was observed among these polymer systems, exhibiting CPN and CPNHA higher temperatures than pNIPAAm. All 3 hydrogels significantly prolonged drug release. The release rate of hydrophilic nalbuphine increased in the order CPN < CPNHA < pNIPAAm. The drug release of these hydrogels exhibited an opposite trend to that of lipophilic drugs.

2.1.3. Xyloglucan

While native xyloglucan is not a thermosensitive polymer, partially degalactosylated xyloglucan does present this behavior. The native polysaccharide has a backbone consisting of glucose residues, with side groups of xylose attached through glycosidic linkage Fig (**2E**). Certain xylose residues are additionally substituted with galactose or the disaccharide galactose-fucose. Xyloglucan can be transformed in a thermosensitive polymer by using a fungal β-galactosidase in order to remove more than 35% of the galactose residue [36].

While tissue engineering applications of xyloglucan are not extensive, it has been used as skin patches [37], oral and rectal drug delivery systems and intraperitoneal injections [38]. Besides, xyloglucan gels were used as sustained release vehicles for the intraperitoneal administration of mitomycin. When it was drug loaded in the two intraperitoneal applications, it was found to provide stronger bioavailability of the relevant drug and longer residence times than previous commercial suppositories. Moreover, there was no apparent tissue damage, implying that xyloglucan hydrogel is a biocompatible material that can be implanted non-invasively via injection in tissue engineering applications. Like cellulose derivatives, xyloglucan solutions form gels at low concentrations (1-2 wt%), and this can be advantageous from a toxicological point of view because the resulting amount of administered polymer is low. In addition, xyloglucan is already approved as food additive. However, the relative low transition temperatures of its gels (22-27°C) become a disadvantage when it has to be handled at room temperature.

Other interesting study was conducted by Itoh *et al.* [39] by preparing *in situ* gelling xyloglucan/pectin formulations for oral sustained drug delivery. This study has examined the gelation and release properties of mixtures of xyloglucan, which has thermally reversible gelation characteristics, and pectin, which gelation is ion responsive. The effect produced by the addition of pectin (0.75 wt%) on the rheological properties of gels formed from solutions of xyloglucan (1.5 and 2.0 wt%) was a significant increase in the gel strength. Visual evaluation of the contents of the rat stomach at different time intervals after oral administration showed that the inclusion of pectin in the xyloglucan solutions was

sion of pectin in the xyloglucan solutions was effective in reducing gel erosion, so sustaining drug release.

2.2. Proteins

2.2.1. Collagen and Gelatin

Biomaterials made of proteins are attractive because of their programmable, biodegradable and bioresorbable nature [40]. A classic hydrogel-forming protein is gelatin, which is derived from animal collagen by treatment at extreme pH followed by heating. Both gelatin and collagen are biocompatible and biodegradable materials widely used for pharmaceutical and medical applications [41]. However, the variability in the composition and structure of animal-derived gelatins, and the possibility that collagen and gelatin can elicit inflammatory responses in humans, urged the development of techniques for the recombinant production of these biomaterials [42,43]. A major advantage of recombinant production is the ability to genetically control the protein structure and thereby, its physical and chemical properties [44].

In humans, 25 distinct collagen types have been identified to date on the basis of protein and/or DNA sequence information. Collagen molecules in physiological solutions will spontaneously self-assemble into higher-order structures [45,46]. The fibril-forming collagens form highly ordered thread-like aggregates solely on the basis of their biophysical properties. As described above, recombinant collagens self-assemble into ordered biological structures or fibrils. Thus, any desired physical and structural forms (e.g., porous matrices, films, gels, or monofilaments) that can be elaborated from tissue-derived collagens can also be produced using recombinant collagens. Drugs may be incorporated into or added after the construction of the final forms.

Gelatin is a generic term for a mixture of purified protein fractions obtained either by partial acid hydrolysis (type A gelatin) or by partial alkaline hydrolysis (type B gelatin) of animal collagen. Gelatin may also be a mixture of both types. Below 25°C, an aqueous gelatin solution solidifies due to the formation of triple helices and a rigid three-dimensional network. When temperature rises above approximately 30°C, changes in conformation from a helix to a more flexible structure make the gel to become liquid again. As the opposite thermal behavior is necessary for biomedical applications, researchers have combined gelatin with other polymers that show thermal gelation closer to the body temperature. Werten *et al.* [47] reported on the genetic design, recombinant production and characterization of a new class of ABA triblock copolymers forming thermosensitve gels with controllable and predictable properties. Gel formation is obtained by combining collagen-inspired (Pro-Gly-Pro)n end blocks (T), which have triple helix-forming ability, with highly hydrophilic random coil blocks defining the distance between the trimer forming end blocks. These monodisperse triblock copolymers have a defined molecular weight, and controllable physical chemical properties. Moreover, they form gels with a molecular architecture that is much more defined than that of traditional gelatins.

Recently, Teles *et al.* [48] have studied the release of entrapped protein from transient gels made of thermosensitive, collagen-inspired ABA triblock copolymers with tailorable properties and with mid blocks of two different lengths (~37 kDa and ~73 kDa). These polymers were produced as heterologous proteins by recombinant yeast. By varying polymer length and concentration, the elastic properties of the hydrogels as well as their mesh size, swelling and erosion could be handled. The authors concluded that the encapsulated protein was quantitatively released, which demonstrates that these hydrogels offer a great potential as drug delivery systems.

3. SYSTEMS BASED ON N-ISOPROPYLACRYLAMIDE

pNIPAAm is a typical thermosensitive polymeric material Fig (**3A**), which exhibits a reversible thermoresponsive phase transition in an aqueous solution and around the LCST (32°C for pure pNIPAAm) [49]. Homogeneous pNIPAAm–water solution becomes opalescent at above 32–33°C due to the collapsing of pNIPAAm chains and the formation of a new pNIPAAm-rich phase [50]. In such transition, hydrogen interactions between pNIPAAm and water are broken and the isopropyl groups become more exposed [51]. So, the hydrophilic behavior of pNIPAAm (below 32°C) changes to a hydrophobic one (above 33°C). During the transition, hydrogels of pNIPAAm present a significant change in volume [52,53]. This phase transition is reversible and occurs within a narrow temperature range [54]. Based on the LCST behavior, several pNIPAAm-containing block copolymers have been used as a novel drug carrier in the field of drug target [55, 56]. This copolymer, consisting of a hydrophilic outer shell of hydrated pNIPAAm segments and a hydrophobic inner core, can form a core–shell micelle structure. The simplicity of the micelle formed by self-assembly of amphiphilic block copolymers and the drug encapsulations by physical mixing are extremely attractive features of polymeric micelles. The hydrophilic–hydrophobic transition of pNIPAAm is well reported in the literature [57]. By copolymerization of pNIPAAm with more hydrophilic monomers, for instance acrylic acid (AAc) or acrylamide (AAm), the value of LCST can be tailored to occur close to the body temperature [58]. In this way, in the 80s Hoffman *et al.* [59] proposed the application of hydrogels made of pNIPAAm (homo and/or copolymers) in the drug delivery field. In such application, it was proposed that a drug, homogenously distributed in the thermosensitive hydrogel below the LCST, leaves the hydrogel after the contraction of the matrix at a temperature above the LCST. Consequently, the drug would diffuse from the shrunken hydrogel to the body if the hydrogel matrix is placed within the body (e.g., as an implant).

The LCST of the polymer needs to be increased to slightly above 37°C to achieve the required properties for drug delivery. This can be monitored by the copolymerization of pNIPAAm with hydrophilic monomers in such a way that a copolymer composition is produced which would undergo transition temperature above 37°C [60, 61]. Several combinations of pNIPAAm with hydrophilic monomers such as acrylic acid, acrylamide, N-vinyl-2,2-pyrrolidone and N-methyl acrylamide can be used to a tailored polymer composition for required applications [62]. It was observed that acrylamide, N-methyl-N-vinylacetamide, N-vinylacetamide and N-vinyl-2-pyrolidone are capable of raising the transi-

tion temperature to a value higher than 37°C [63]. Coughlan *et al*. [64] reported the effect of drug physical chemical properties on swelling/deswelling kinetics of a pNIPAAm hydrogel as well as on the pattern of pulsatile drug release. In particular, drug solubility, size and chemical nature were critical parameters. The hydrogel swelling rate was decreased by the presence of hydrophobic drug and may be increased by the osmotic influence of hydrophilic drug molecules.

3.1. Poly (N-Isopropylacrylamide-Co-Acrylic Acid)

An interesting study was performed by Na *et al.* [65] to assess the efficacy of poly(N-isopropylacrylamide-co-acrylic acid) (p(NiPAAm-co-AAc)) Fig. (**3B**) as an injectable drug delivery vehicle and as a cell therapeutic agent in the form of a supporting matrix for the chondrogenic differentiation of rabbit chondrocytes. The p(NiPAAm-co-AAc) hydrogel itself without specific differentiation-inducing drugs was used as a control in order to determine the effects of these materials on chondrogenic differentiation. The level of cartilage associated to extracellular matrix (ECM) proteins was examined by immuno histochemical staining for collagen type II as well as by Safranin-O and Alcian blue (GAG) staining. These results highlighted the potential of a thermoreversible hydrogel mixed with chondrocytes and differentiation materials as an injectable delivery vehicle for use in neocartilage formation. On the other hand, Ikram *et al.* [66] have investigated recently the effect of radiation-induced graft copolymerization of pNIPAAm and acrylic acid mixture on polypropylene nonwoven fabric to develop a thermosensitive material. The grafting was carried out using methanol, acetone and butanone as homopolymerization inhibitors in the reaction medium. It was observed that the grafting was significantly influenced by the reaction conditions, such as radiation dose, monomer concentration, monomer ratio, solvent composition and reaction temperature. The degree of grafting increased along with the AA and pNIPAAm concentration in the reaction medium and with the AA fraction in the pNIPAAm/AA mixture. The temperature of the grafting process depends strongly on the thermosensitive nature of the grafted chains. The authors suggested that it is possible to design a proper graft copolymer matrix by properly varying the radiation and grafting conditions. More information on the characterization and the thermoresponsive behavior of the fabric is needed to establish the correlation between the grafted levels and the performance in the delivery of bioactive components.

3.2. Poly (N-Isopropylacrylamide)/Poly (Ethylene Oxide)

A new family of polymers that self-assemble to form thermoreversible gels has been reported by Lin and Cheng [67]. It is composed by linear block copolymers and a star, with a central hydrophilic segment poly (ethylene oxide) (POE), and terminal pNIPAAm segments, sensitive to the temperature. Linear and star copolymers of POE and pNIPAAm form liquid aqueous solutions at room temperature, which produce relatively strong elastic gels with heating. It was found that rheological properties of hydrogels depend on molecular architecture. Moreover, the star structure with four pNIPAAm terminal segments showed the best characteristics. These copolymer solutions have low to moderate viscosity for injection, high gel strength, low degree of syneresis, and fast gelation kinetics. However, these systems have not been yet investigated for biomedical purposes.

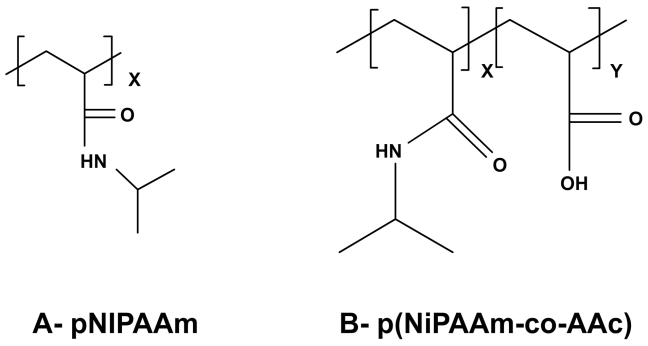


Fig. (3). Some chemical structures of the units of thermosensitive polymers used to obtain systems based on N-isopropylacrylamide.

3.3. Poly(N-Isopropylacrylamide)/ Polysaccharides

A novel thermosensitive *in situ* gel-forming copolymer, pNIPAAm/chitosan (pNIPAAm/CS), was studied [68]. pNIPAAm/CS had a LCST of 32°C, which is close to the surface temperature of the eye. The Cmax of timolol maleate in aqueous fluid for the pNIPAAm/CS solution was 11.2 μg/ml, which is two-fold higher than that of the conventional eye drop, along with a greater AUC. Furthermore, the pNIPAAm/CS gel-forming solution of timolol maleate had a stronger capacity to reduce the intra-ocular pressure (IOP) than that of the conventional eye drop at a same concentration over a period of 12 h. Another interesting approach for obtaining a double hydrophilic graft copolymer dextran-graft-poly(N-isopropylacrylamide) was proposed by Tan *et al.* [69] . The authors reported a novel nano drug-loading system that was stabilized by hydrogen bonds between the host polymer and the guest molecules, and that showed novel thermosensitive drug release behavior. At the temperature above the LCST, the dextran-graft-pNIPAAm forms uniform nanoparticles in aqueous solution [70]. When the temperature is below the LCST, this copolymer should molecularly dissolve in the aqueous solution because both the backbone and the side chains are hydrophilic. However, previous studies performed by these authors indicated that loose aggregates of unimers can be found even below the LCST [71]. The authors suppose that this behavior may be caused by the selective solvation of water towards the backbone and the side chains. This molecular aggregation below the LCST was also found in another double hydrophilic copolymer pNIPAAm-block-PEG, and the same explanation was given [72, 73]. This approach extends the theory of polymeric aggregation and may be useful to design new colloidal carriers.

4. POLOXAMER-BASED SYSTEMS

4.1. Poloxamer (Pluronic®)

In the past two decades, the development of efficient delivery systems for biological agents, such as low molecular weight drugs and biomacromolecules (DNA, proteins, among others), has attracted enormous attention. It is be-

lieved that these systems will help to overcome previously encountered barriers in target sites, as well as to increase the solubility and stability of delivered biological agents. Synthetic polymers are among the main materials used in drug and genes [74] delivery systems. Important and promising examples of these materials are triblock copolymers also known as Pluronic or Poloxamer Fig. (**4A**), which have a thermoreversible behavior in aqueous solutions. These polymers consist of blocks of ethylene oxide (EO) and propylene oxide (PO) arranged in a basic structure ABA: OEx-OPy-OEx. This arrangement results in an amphiphilic copolymer, where the number of hydrophilic units EO (x) and hydrophobic units OP (y) can be altered. The copolymers with different x and y values are characterized by different hydrophilic-lipophilic balance (HLB). Poloxamer series cover a wide range of liquids, pastes and solids, with molecular weights and weight ratios of PO-EO varying from 1,100 to 14,000 and from 1:9 to 8:2, respectively. By adjusting composition, molecular weight and concentration, reversible gelation can occur at physiological temperature and pH [75].

A distinctive characteristic of poloxamers is the ability of each copolymer molecule to self-assemble forming micelles in aqueous solution. Poloxamers form a molecular dispersion in water at copolymer concentrations below the critical micelle concentration (CMC). Above the CMC, the molecules begin to aggregate, forming micelles through a process known as "micellization". The driving force for micellization is the hydrophobic interaction of PO blocks. These blocks are self-assembled in the inner core of micelles covered by a hydrophilic crown of EO blocks. On the other hand, micelle formation has a strong dependence on temperature. Below certain temperature, known as critical micellar temperature (CMT), both blocks of ethylene oxide and propylene are hydrated and poly (PO) is relatively soluble in water. With increasing temperatures, the chains of poly (PO) become less soluble, favoring micelle formation [76]. Poloxamer micelles are commonly represented as spheres composed of a core of PO and a crown of EO.

The transfer process of water-insoluble compounds to the core of the PO in the micellar solution is known as "solubilization". Poloxamer micelles containing solubilized drug of low molecular weight and polypeptides have been actively investigated as possible drug delivery systems [77]. The core formed by PO chains is a compartment incompatible with water, which is separated from the aqueous exterior by the hydrophilic crown of EO chains, forming a "load compartment" able to incorporate many biological agents. As a result, polymeric micelles can be used as efficient carriers of compounds with low solubility, undesirable pharmacokinetics and low stability in a physiological environment [78]. The hydrophilic crown makes an important contribution to pharmaceutical behavior. Copolymer formulations allow to maintain the micelles in a state of dispersion, as well as to decrease undesirable drug interactions with cells and proteins through steric stabilization effects.

The gelation mechanism of copolymers in aqueous solutions has been extensively studied [79], but it is still a matter of discussion. Different studies have clearly indicated a micellar mode of association [80,81]. Micelle formation occurs at the critical temperature of micellization due to dehydration of the PO blocks [82]. With increasing concentration, the micellization becomes more important, and at a certain concentration, the micelles come in contact and move no more. In addition, the formation of highly ordered structures, such as a cubic crystalline structure, has been proposed as the driving force of the gel formation, but this hypothesis has been recently questioned. Thus, the packaging and the entanglement of micelles could be possibly explained by the gelation mechanism of the Poloxamer solutions at increasing temperature and concentration. Poloxamer 407 (Pluronic® F127) showed the ability of forming gels at 25°C at 20 wt% concentration, which is a lower value than the reported concentrations for other members of the Poloxamer series. At room temperature (25°C), their solutions behave as a viscous mobile liquid, while they look as a semi-solid transparent gel at body temperature (37°C).

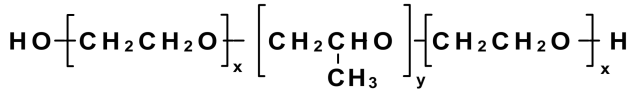
Potential disadvantages of poloxamer gels are their low mechanical strength, rapid erosion (meaning dissolution from the surface). In spite of the non-degradable nature of these materials, molecules of molecular weights < 10-15 kDa may be eliminated through renal filtration.

Poloxamer 407 is generally recognized as non-toxic and preliminary data indicate that this copolymer would be well tolerated [83]. However, several studies have reported systemic adverse effects [84-86]. Taken together, these results have led Poloxamer 407 use to design medical, pharmaceutical and cosmetic systems. In the past 15 years, this copolymer has been extensively investigated for various applications. Although the purpose of this work is not to review all of them, some recent applications are discussed below. Poloxamer copolymers can be used as soluble media for otherwise insoluble drugs as well as nano-containers for site-specific drug delivery in body tissues. The various properties of Poloxamer copolymers can also improve drug performance, because they act as enhancers of the biological membrane improving the response directly on the target cells. Poloxamers represent a bio-inert environment, due to the hydrophilicity and flexibility of the POE chains. Therefore, most cells do not grow on these polymers, so they can be used as tissue adhesion barriers. Poloxamer 407 has a rapid gelation at 37°C after incubation for 1 min, at 30 wt% in cell culture medium [87]. The use of this polymer was also reported for tissue engineering applications. For example, Poloxamer 407 was evaluated as scaffold for lung tissue engineering, showing promising results on tissues growth with a low inflammatory response [88]. Poloxamer gels can enhance drug release compared with their solutions, but the release period rarely exceeds a few days [89]. This property makes Poloxamer gels interesting for short-term therapies, such as pain treatment [90], infection treatment [91], covering burn wounds [92] and fertility control [93]. Recently, Poloxamer copolymers have shown promising potential for gene therapy [94-99].

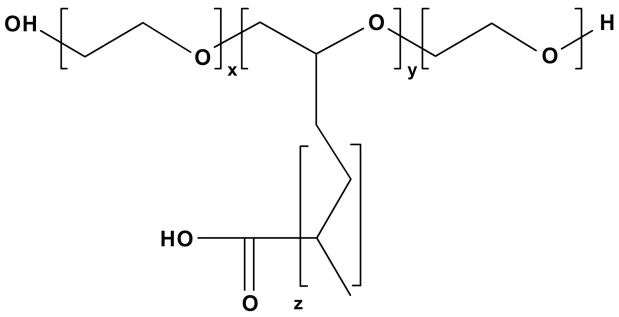
Besides injectables, other routes of administration have been evaluated for these polymers, such as rectal [100], vaginal [101], transdermal [102] and ophthalmic [103]. As a general rule, Poloxamer formulations increase the residence time of drugs in application sites, resulting in an improvement of bioavailability and effectiveness.

4.2. Poloxamer/Poly (Acrylic Acid)

Poly (acrylic acid) (pAA) of high molecular weight is a known bioadhesive polymer that adheres to the moist mucous of lining cells of eyes, nose, lungs, gastrointestinal tract and vagina [104]. It is often incorporated into drug delivery systems that come in contact with mucosal surfaces to enhance residence times. However pAA by itself is not a thermosensitive polymer and for this reason its modification and combination with other polymers was studied. Bromberg (1998) [105] developed poloxamer-g-pAA hydrogels Fig. (**4B**) and evaluated their rheological properties. He found that temperature-induced sol–gel transition and gel strength were concentration-dependent. An increase in polymer concentration resulted in lower transition temperature and higher gel strength. The process of synthesis of the poloxamer-g-pAA copolymer described by the authors consisted of the Poloxamer activation by derivatization with 4-nitrophenyl formate in the presence of triethylamine. After purification, the intermediate was reacted with diaminoethylene to yield an amino terminated Pluronic which was conjugated to poly-(acrylic acid) via an amide bond applying dicyclohexylcarbodiimide (DCC) as a coupling agent.



A- Poloxamer or Pluronic



B- Poloxamer-g-pAA

Fig. (4). Some chemical structures of the units of thermosensitive polymers used to obtain Poloxamer-based systems.

Besides polymer concentration, pH and salts have influenced gelation properties [106]. By increasing pH, the onset of gelation was shifted to lower temperatures and the gel strength increased. The bioadhesive nature of this system makes it interesting for a wide variety of applications. The hydrogels of Poloxamer/pAA have been proposed for drug delivery by vaginal route [107] and topical administration [108].

More recently, Ma *et al.* [109] have designed systems to prolong the precorneal residence time and to improve ocular bioavailability of the drug. Poloxamer 407-g-poly(acrylic acid) copolymers were studied as *in situ* gelling vehicle for ophthalmic drug delivery system. Drug release rates decreased when acrylic acid/Poloxamer molar ratio and copolymer solution concentration increased. *In vivo* experiments showed that the drug residence time and the total resident amount in rabbit's conjunctiveal sac increased by 5.0 and 2.6 folds for *in situ* gels compared to eye drops. The authors concluded that *in situ* gels containing Poloxamer/pAcopolymer may significantly prolong the drug residence time and thus improve bioavailability.

4.3. Poloxamer/Natural or Semi-Natural Macromolecules

The chemical modification of Poloxamer has been reported with encouraging results, being obtained gels with less erosion and suitable gelation temperatures. However, chemical modification usually introduces toxic residues and so; the safety of new polymers is questioned [110,111]. On the other hand, the addition of macromolecules of natural or semi-natural origin in the Poloxamer gel is more cost effective and convenient, providing an alternative method to obtain gel composite systems with improved sustained release properties and security. Moreover, these macromolecules are usually capable of forming noncovalent bonds with the mucus that covers the epithelial tissues, thus prolonging the *in vivo* residence time of release platforms. For example, the effect of hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose (CMC) and dextran on the *in vitro* release of lidocaine from Poloxamer 407 composed gels was studied [112]. The authors observed that the addition of the different macromolecules into the Poloxamer did not produce a significant improvement in the polymer behavior. Also, Bermudez and Grau [113] obtained promising results by combining Poloxamer with carrageenan in order to obtain an injectable depot system for veterinary use, using progesterone as model drug.

On the other hand, studies to evaluate the combination of Poloxamer and chitosan were also performed. The results showed that the release of the drug applied was improved not only at eye level, but also at buccal [114,115]. Recently, a thiolated dextran (Dex-SH) with a degree of substitution of 10 was synthesized and used for *in situ* hydrogel formation via Michael-type addition using vinyl sulfone functionalized Pluronic 127 or acrylated Pluronic 127 [116]. Dextran/Pluronic hydrogels were rapidly formed *in situ* under physiological conditions. These hydrogels showed short gelation times and their mechanical properties could be adjusted by varying the Pluronic concentration or the temperature. The authors suggested that dextran/Pluronic hydrogels are promising for biomedical applications.

4.4. Poloxamer 407/Poloxamer 188

Neither Poloxamer 407 nor Poloxamer 188 solutions possess the appropriate gelation temperature (Tgel) for their application as drug delivery systems. These copolymers show gelation temperatures higher than 40°C at low concentrations (~ 10 wt%) but lower than 25°C at high concentrations (~ 30 wt%). However, by selecting poloxamer mixtures at specific concentrations, it is possible to handle the gelation temperature to obtain a value suitable for this kind of application, i.e. near to body temperature (37°C) [117]. Mayol *et al.* [118] have developed a novel Poloxamers/hyaluronic acid

in situ forming hydrogel for drug delivery. In order to evaluate the feasibility of these platforms for drug delivery, the optimized systems were loaded with acyclovir and their *in vitro* release properties were studied. By formulating Poloxamers/hyaluronic acid platforms at specific concentrations, it was possible to obtain a thermoreversible gel with a Tgel close to body temperature. The addition of hyaluronic acid did not hamper the self assembling process of poloxamers delaying the gelation temperature just a few Celsius degrees. *In vitro* release experiments indicated that the optimized platform was able to prolong and control acyclovir release for more than 6 h. Recently, Xuan *et al.* [119] performed a series of studies on the rheological characterization and the *in vivo* evaluation of thermosensitive Poloxamers hydrogels for intramuscular injection of piroxicam. Poloxamers hydrogels containing piroxicam as a model drug were prepared with poloxamers, sodium hydroxide and sodium chloride by the "cold method". Among the tested compounds, sodium hydroxide and piroxicam decreased the viscosity and retarded the gelation time of the injectable gel. However, sodium chloride did the opposite. The thermosensitive injectable gel composed of 2.5 wt% piroxicam, 15 wt% Poloxamer 407, 17 wt% Poloxamer 188, 0.01 wt% sodium hydroxide and 1.6 wt% sodium chloride was easy to administer intramuscularly and gelled quickly in the body. Furthermore, it kept the plasma concentration of the drug for 4 days and gave a 150-fold higher AUC compared to piroxicam solution. On the other hand, Shastri *et al.* [120] have designed and developed a thermoreversible ophthalmic *in situ* hydrogel for Moxifloxacin HCl delivery using a combination of poloxamer 407 and poloxamer 188 with different mucoadhesive polymers such as Xanthan gum and Sodium alginate. The authors found that these systems were effective and safe for ocular drug delivery.

5. OTHER SYNTHETIC POLYMERS

5.1. Copolymers of Poly(Ethylene Glycol)/Biodegradable Polyester

Poly(ethylene glycol) (PEG) is generally a linear-chained polymer consisting of an ethylene oxide repeating unit $(–O–CH_2–CH_2)_n$ Fig. (**5A**). The ease, with which PEG may be modified, whether with cross-linkable groups for network formation or with degradable groups for resorbable applications, has probably led to the widespread interest of PEG for tissue engineering and other biomedical applications. For example, PEG has been copolymerized with PLGA as well as with alginate to form hydrogels. It has been prepared a thermosensitive microgel, composed of poly (ethylene glycol-(d, l-lactic acid-co-glycol acid)-ethylene glycol) (PEG–PLGA–PEG) triblock copolymers Fig. (**5B**), which had the property of being a liquid at room temperature but solidifying at body temperature [121]. Once solidified, the gel slowly degraded over the course of 30 days, releasing its oligo-nucleotide components to the surrounding cells. Possible applications of this gel system to wound healing are being pursued.

In the 90's MacroMed Inc. discovered that the thermosensitive sol–gel transition of the copolymer/water system is directly related to the block composition and the arrangement of the copolymer [122,123]. After replacing the PLA block with PLGA block, modifying the block length of PEO and rearranging the block sequence, MacroMed reported that both mPEG–PLGA–mPEG and PLGA–PEG–PLGA (Regel®) Fig. (**5C**) are thermosensitive liquid drug carrier systems which can be loaded with therapeutic agents at a temperature lower than 30°C with a sol–gel transition at 37°C. Regel® has been extensively studied due to the ease of its one-step synthesis. Unfortunately, Regel® system is usually required to be prepared at a temperature lower than room temperature for injectable administration and it was reported to control the release of loaded proteins for only 7 days. Further increasing of the length of hydrophobic PLGA blocks caused protein aggregation in the formulations [124]. On the other hand, Chen *et al.* [125] developed a system based on triblock PLGA-PEG-PLGA for controlled release of testosterone. The gelling properties were influenced by the PLGA and PEG proportions. More recently, Tang and Singh [126] have developed a suitable controlled release system for proteins by modifying the structure of the thermosensitive copolymer monomethoxy poly(ethylene-glycol)-co-poly(d,l-lactide-co-glycolide)-co-monomethoxy poly(ethylene-glycol) (mPEG–PLGA–mPEG). They modified the structure varying the block length of mPEG–PLGA–mPEG copolymer. Eleven mPEG–PLGA–mPEG triblock copolymers were synthesized having serially increased length of both hydrophilic mPEG and hydrophobic PLGA block, in order to find a copolymer consisting of the longest hydrophobic PLGA block while retaining the system's injectability at room temperature, sol–gel transition property at 37 ◦C and satisfactory gel stability. The copolymers controlled the *in vitro* release of lysozyme conserving protein stability and biological activity, which makes this delivery system appropriate for long term controlled release of proteins.

5.2. Derivatives from Poly(Organophosphazene)

Poly(organophosphazenes) (PPZ) Fig. (**5D**) have been suggested as potential thermosensitive hydrogels for use in the development of injectable gel-depot systems. Current advances in PPZ include their use in drugs [127] and cells [128] delivery systems. Recently, Chun *et al.* [129] reported an injectable and biodegradable thermosensitive PPZ that bear both hydrophobic and hydrophilic properties. Various hydrophobic, hydrophilic and other substituents could be introduced into the polymer backbone, which provides easy control over the hydrogel characteristics. Most of the synthesized PPZ displayed a sol–gel phase transition behavior in an aqueous solution with temperature changes. It is also known that the PPZ hydrogels produce non-toxic biodegradable products, such as H_3PO_4, NH_4^+, PEG, amino acids, and have good biocompatible properties [130]. On the other hand, Kang and Song [131] have evaluated the effect of chitosan on the release of protein from thermosensitive PPZ hydrogels. Under biological conditions, hydrophilic model protein drugs, including bovine serum albumin (BSA), gelatin type B (MW 20,000) (GB20), and fluorescein isothiocyanate albumin (FITC- albumin) loaded in the hydrogels were released for 1–2 weeks, showing an initial burst release. However, this initial burst release could be suppressed when the proteins were couched in a complex with chitosan, and under these conditions the release period was prolonged. BSA, GB20, and FITC-albumin, all of which are negatively

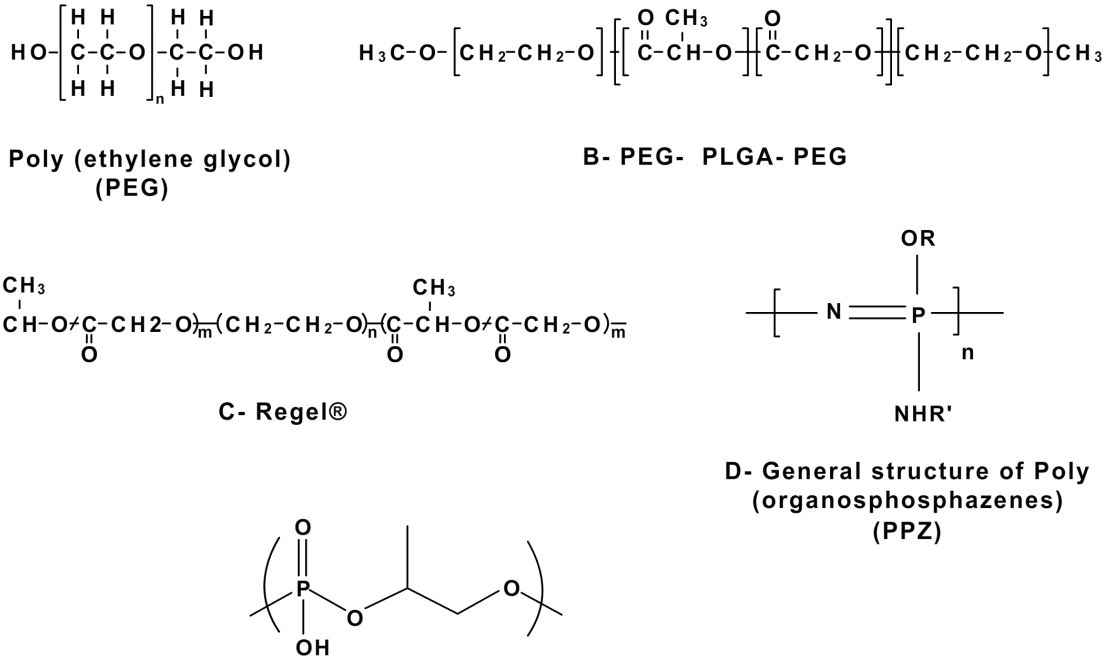


Fig. (5). Some chemical structures of the units of thermosensitive synthetic polymers.

charged at a pH of 7.4, interacted with chitosan harboring positive amine groups. The appropriate ratio of proteins to chitosan for suppression of the initial burst was 1:5 to 1:10. The authors concluded that both the release rate and the release period could be controlled via the formation of protein/chitosan complex. Recently, Park *et al.* [132] have developed controlled and sustained protein release formulations using a system composed of polyelectrolyte complexes (PECs) and thermosensitive PPZ hydrogels as an injectable gel-depot system. The results obtained suggested that the PEC-loaded injectable and thermosensitive PPZ hydrogel has considerable potential for creating a sustained protein delivery system by using the PEC via electrostatic interaction.

5.3. Poly (1,2-Propylene Phosphate)

A new system of injectable thermosensitive hydrogels was proposed by Wang *et al.* [133]. The system is based on a synthetic polyanion, poly (1,2-propylene phosphate) Fig. (**5E**), which can be crosslinked by calcium ions. Solutions of poly(1,2-propylene phosphate) in water did not exhibit temperature-dependent phase transition. In the presence of $CaCl_2$, the polymer solutions remained liquid at room temperature, but gelled rapidly when heated. The sol–gel transition temperature was found to be dependent on polymer and Ca^{+2} concentrations. Further studies are needed to evaluate the feasibility of this system to use it in pharmaceutical and tissue engineering fields.

6. CONCLUSIONS

The usefulness of thermosensitive gels in drug delivery and biomedical applications is immense and it increases over time. Research in the area of thermosensitive polymers for drug and gene delivery, as well as in tissue adhesion prevention and wound treatment, has been well established in recent years. However, the development of these polymer platforms must to overcome challenges related to the improvement of drug stability and release kinetics and to the optimal administration conditions. Although each application has different requirements, this contribution discussed a great variety of possible methods to adjust gel properties to match a specific use. The choice of a particular thermosensitive polymer depends on its intrinsic properties and the intended therapeutic use. For example, the formation of a transparent gel is especially important when considering ophthalmic applications. Non-biodegradable gels could be useful for other administration routes than the parenteral.

Thermoreversible gels can be prepared with naturally occurring polymers. Polysaccharides usually show good biocompatibility and/or biodegradability and the cellulose derivatives, chitosan and xyloglucan solutions are thermosensitive at low polymers concentrations.

However, these systems cannot be adapted for sustained release of hydrophilic drugs of low molecular weight due to the large size of its hydrated pores which allows a rapid diffusion. On the other hand, they provide appropriate scaffolds for cell growth and tissue repair.

The hydrogels PEO/PLGA are systems particularly attractive for pharmaceutical applications. They are biodegradable and generally have a good safety profile. Their composition can be adjust to provide sustained release of drugs during weeks or months.

Perhaps, Poloxamer hydrogels represent the most studied system. Nevertheless, despite the clinical acceptance of poloxamer as a pharmaceutical excipient, these polymers have not met the initial expectations as pharmaceutical and

biomedical implants, mainly due to its low degree of biodegradability and the incapacity to provide sustained drug delivery for longer periods than a few days. However, as discussed, recent developments in the design of poloxamer systems showed that some of these problems could be overcome. A great advantage of amphipathic molecules, such as Poloxamer 407 and PEG-PLGA-PEG, is that water can be used as a solvent, which is by definition, the preferred solvent for parenteral purposes.

Further progress in the development of biotechnology and drugs will produce more pharmaceutical active agents which will be difficult to administer by conventional routes, so it is expected to increase the demand for controlled release systems or site-specific systems.

These systems can be potentially useful for providing a wide variety of therapeutic agents difficult to formulate, such as DNA, protein and water-insoluble or high toxic drugs. Recently, gels exhibiting a sol-gel thermosensitive behavior have been reported as carriers of cells for tissue regeneration.

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