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Review article

Polyethylene glycol (PEG)–Poly(N-isopropylacrylamide) (PNIPAAm) based thermosensitive injectable hydrogels for biomedical applications

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ABSTRACT

Protein and peptide delivery by the use of stimuli triggered polymers remains to be the area of interest among the scientist and innovators. In-situ forming gel for the parenteral route in the form of hydrogel and implants are being utilized for various biomedical applications. The formulation of gel depends upon factors such as temperature modulation, pH changes, the presence of ions and ultra-violet irradiation, from which drug is released in a sustained and controlled manner. Among various stimuli triggered factors, thermoresponsive is the most potential one for the delivery of protein and peptides. Poly(ethylene glycol) (PEG) based copolymers play a crucial role as a biomedical material for biomedical applications, because of its biocompatibility, biodegradability, thermosensitivity and easy controlled characters. This review, stresses on the physicochemical property, stability and compositions prospects of smart thermoresponsive polymer specifically, PEG/Poly(N-isopropylacrylamide) (PNIPAAm) based thermoresponsive injectable hydrogels, recently utilized for biomedical applications. PEG–PNIPAAm based hydrogel exhibits good gelling mechanical strength and minimizes the initial burst effect of the drug. In addition, upon changing the composition and proportion of the copolymer molecular weight and ratio, the gelling time can be reduced to a great extent providing better sol–gel transition. The hydrogel formed by the same is able to release the drug over a long duration of time, meanwhile is also biocompatible and biodegradable. Manuscript will give the new researchers an idea about the potential and benefits of PNIPAAm based thermoresponsive hydrogels for the biomedical application.

1. Introduction

The administration of the proteins and peptide through parenteral routes is the most preferred one since a long time. However, frequent administration had led to poor patient compliance due to pain and irritation. Even though, there are various other routes for the delivery of protein and peptides such as transdermal; vaginal; intranasal and intra-pulmonary routes, among them is parenteral route always designated as the main area of interest [1–3]. The extensive research had evolved the invention of long acting injections and implants [4–7] to prolong the release of proteins and peptides for extended duration of time. HG,[4] due to their insoluble polymers network help to retain shape and therefore, suitable for the loading of the bioactive [8]. Injectable hydrogels are triggered by temperature, which remain fluid at room temperature and transform to viscous gel, as the temperature rises [9]. These gelling systems sustain the drug release to larger extent and subsequently increase the bioavailability by providing local effect. Injectable hydrogels were prepared by a series of thermoresponsive (or reversible) triblock copolymers comprising of poloxamer and PEG.[5] Characteristically, poloxamer shows reversible gelification upon repeated cooling and warming [10], hence best suited for biomedical applications [11–13]. However, the hydrogels prepared with Poloxamers have its own limitation regarding its biodegradability. Thus, there is a need for an alternative biomaterial required to prepare the hydrogel, which must be biocompatible along with safety and efficacy.

Out of various stimuli-triggered external factors such as, temperature [14–16], pH, electric and photofields [17–19],

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temperature stimuli triggered hydrogel remain the most studied and preferred one for the controlled drug delivery [20]. These hydrogels have proven to play a vital role for the delivery of bioactives. More specifically, PEG based hydrogel comprising from the blocks of hydrophobic polyesters such as PLGA[6] and PCL[7] has gain more responsiveness in the recent past, because of its good biodegradability and biocompatibility properties in contrast with those of Poloxamers [21]. Among the above-mentioned polymers, PNIPAAm[8] because of its LCST[9] of 32 °C, remains to be the most suitable temperature sensitive polymer. PNIPAAm based hydrogels can be prepared by either chemical or physical crosslinking method. Among these two methods, chemical crosslinking method is preferred because of its ease in manufacturing by tuning/altering the initiator ratio; crosslinking agents; precursor ratio and concentration. Some crosslinking agents and initiator show toxicity, which need to be removed further [22]. In addition, hydrogels formed by chemical crosslinking method are generally nonbiodegradable. To overcome such limitation, hydrogels formed via physical method like through hydrogen or ionic bonds, van der Waal's interactions, crystal formation and/or physical entanglements are most appropriate [23–26].

2. Reason to develop PNIPAAm–PEG hydrogels over simple PNIPAAm hydrogels

Crosslinking design improves the inherent properties of hydrogels. Crosslinking prevents the molecules of the hydrogels from being dissolved in a swelling medium by holding the entire molecule together. The advantage of physical crosslinked hydrogel includes no use of crosslinking agents or initiators. Physical crosslinking includes hydrogen or ionic bonds, van der Waal's interactions, crystal formation and/or physical entanglements [25]. Physically crosslinked hydrogels fail to show strength and at the same time are not stable as covalent crosslinked systems. To improve the same, PNIPAAm is crosslinked with a biocompatible and biodegradable polysaccharide, chitosan by Sun et al. [27]. However, the systems formed were brittle and showed poor physical and mechanical properties. Thus, to improve this, author had incorporated PEG, to improve the mechanical properties of the hydrogels. Chitosan/PNIPAAms hydrogels exhibit lower crystallinity than each individual component, which got higher after the introduction of PEG i.e., chitosan/PEG/PNIPAAm gels. The introduction of PEG activated the crystals as crosslinker and affect the properties of the physically crosslinked hydrogels thereof. According to the results, PEG with 2000 MW[10] showed limited swelling, very few pores were formed because of its high crystalline regions; with 6000 bigger, and more pores were formed because of lower crystallinity of the physical hydrogel. When PEG with MW 10,000 and 20,000 was incorporated into the system, very few pores were formed because of the increased MW of PEG which limits the mobility of PNIPAAm molecules and made it harder even at LCST. Thus, it can be understood that the PEG crosslinked PNIPAAm can improve the physical and chemical properties of the hydrogel up to a great extent [27]. Some of the works patented on the above-related work are summarized in Table 1.

3. Biodegradability and biocompatibility of PNIPAAm-based hydrogels

Biodegradability and non-toxicity are the basic desired properties, when working with the thermogelling block copolymers hydrogels for parenteral delivery. To make PNIPAAm biodegradable and biocompatible the researchers adopted various synthetic approaches. Among them crosslinked cores of the poly(ethylene oxide)-b-poly(N-isopropylacrylamide) (PEO-b-PNIPAAm) micelle with a biodegradable crosslinker BAC[11] forms a stable micelle like nanoparticles. Due to the hydrophobicity of the biodegradable crosslinked BAC, cores of micelles is copolymerized with the NIPAAm. The model drug used for the study (Dox[12]) acts like a fluorescent probe as well as an anti-cancer drug too. The study showed that PEO-b-PNIPAAm-BAC nanoparticles sequester Dox. The outcome of this modification had made it stable up to two weeks even at room temperature and at the same time biodegradable too so that they do not build up the body. Likewise, the PEG-based triblock copolymers are also fulfilling the same, with desired and tunable control over the delivery system. Some of the investigated PEG-based copolymers are discussed here, highlighting the innovators idea behind the development of these copolymers. In addition, PEG is approved by the FDA[13] for the use in pharmacological applications [28]. This polymer is best suited to be applied as an injectable in-situ forming gelling biomaterial whose mechanical properties go beyond those of purely physical gels, however still allows a temperature-triggered gelation. The section includes the synthesis and evaluation parameters of these PEG-based copolymer hydrogels utilized for biomedical applications.

4. Biomedical applications of thermogelling PEG–PNIPAM blocks copolymers

A PNIPAAm-based system due to its phase transition between ambient and body temperature and copolymerization of PNIPAAm with different types of monomers, remains to be one of the most commonly used thermosensitive materials to formulate hydrogels [29]. PNIPAAm exhibits an LCST around 32 °C, making it most suitable polymer for in situ hydrogel [30]. At room temperature it is a free-flowing solution, once the temperature is raised (body temperature) it solidify into an elastomeric hydrogel. Moreover, crosslinked PNIPAAm, owing to its highly swollen nature allows injectability even through small gauge needles [31,32]. PNIPAAm is water-soluble at a temperature below its LCST; though, at a LCST temperature or higher, weak hydrogen bond interaction between PNIPAAm and water tend to release the water from the system. At this stage, PNIPAAm undergoes a coil to globule transition and become insoluble. Thermo-sensitive hydrogels exhibit volume phase transitions or sol–gel phase-transitions at critical temperatures, i.e., LCST or UCST.[14] Some of the LCSTs among several typical thermosensitive polymers are shown in Table 2. The LCST polymers exhibit swelling-to-shrinking (or sol-to-gels) transition with increasing temperature, whereas the UCST systems undergo the opposite transitions. This LCST can be altered by incorporation of various comonomers. In addition, conjugation of hydrophobic monomers leads to a decrease in LCST whereas, addition of hydrophilic monomers will give the reverse result. Poly(NIPAAm) undergoes gelation by physical cross-linking. As already discussed, at temperatures below its LCST, the polymer chains are hydrophilic and thus soluble in the aqueous environment. Gradual increase in hydrophobicity is/was observed as the temperature of the polymer chain is increased above its LCST. Shrinkage of the chains is due to the dispersion of the water present between chains to form a gel [33,34]. Here, the sol–gel transition state is rapid and reversible too. With such fast transition to temperature stimuli, drugs can be quickly released from the hydrogel, exhibiting on–off switching release system [35].

[6] Poly(lactic-co-glycolic) acid.
[7] Polycaprolactone.
[8] Poly(N-isopropylacrylamide).
[9] Lower critical solution temperature.
[10] Molecular Weight.
[11] N,N-bis(acryloyl)cystamine.
[12] Doxorubicin.
[13] Food and Drug Administration.
[14] Upper critical solution temperatures.