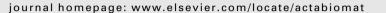
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Comparison of properties between NIPAAm-based simultaneously physically and chemically gelling polymer systems for use in vivo

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ABSTRACT

In this work, a comparison between two different physical-chemical gels, poly(NIPAAm-co-cysteamine) with poly(NIPAAm-co-cysteamine-vinylsulfone) and poly(NIPAAm-co-cysteamine) with poly(NIPAAmco-HEMA-acrylate), is made. These hydrogels undergo gelation via dual mechanisms: temperature sensitivity (physical gelation) and chemical crosslinking (chemical gelation). The advantages of using both gelation mechanisms are to reduce the creep experienced by purely physical gels and to increase the elastic modulus of purely chemical gels. Here, the physical-chemical gels were synthesized and characterized for their chemical, structural, thermal, mechanical and morphological properties. The gels were also tested for their gelation kinetics, swelling, degradation and cytotoxicity. The copolymers were successfully synthesized and their phase transition temperatures fall in a feasible range (29-34 °C) for use in vivo. With rheology, it was shown that use of simultaneous physical and chemical gelation resulted in improved properties, with increased elastic moduli and reduced frequency dependence. The rates of reaction of thiols to vinyls differ between the two systems, demonstrating a greater effect of chemical gelation in one gelling system over the other, due to the faster rate of thiols consumed into reaction. The morphology of the gels proved to be quite different when analyzed by scanning electron microscopy, showing differences in swelling behaviors. Cell studies illustrated good growth of cells exposed to the gels. Both hydrogels, although possessing slight differences, demonstrate the capability of being injected in vivo for use as embolic agents for occlusion of aneurysms.

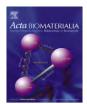
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1. Introduction

Stimuli-responsive materials have attracted much attention from scientists and engineers due to their ability to adapt to environments when presented with various cues. These materials have the advantage of changing their form according to the environment and applied stimuli. Amongst the different forms of stimuli which have been investigated, temperature sensitivity has been widely researched. Thermoresponsive materials can undergo a phase transition change, either a gel-sol or sol-gel, at a specific temperature called the lower critical solution temperature (LCST) [1]. One particularly popular thermoresponsive material is poly(*N*-isopropyl acrylamide), or poly(NIPAAm), due to its phase transition temperature being around 31 °C [2]. With an LCST close to physiological temperature, this material has thus found prominent use in biomedical applications. This LCST can be altered by incorporation of various comonomers. Conjugation of hydrophobic monomers leads to a decrease in LCST, whereas addition of hydrophilic monomers results in an increase in it [3-6]. Groups have employed poly(NIPAAm) and its copolymers for different applications, including cell and enzyme immobilization, controlled drug delivery and gene delivery, bioconjugation, protein dehydration and embolization [7,8].

Poly(NIPAAm) undergoes gelation by physical cross-linking. At temperatures below its LCST, the polymer chains are hydrophilic and soluble in the aqueous environment. As the temperature is increased above its LCST, the polymer chains become hydrophobic, allowing for the expulsion of water molecules [9]. As the water present between chains is dispersed, the chains can then collapse upon themselves to form a gel at sufficient concentrations. The association of the NIPAAm chains is not fully understood; however, it can occur through various forces seen in reversible physical gels, such as molecular entanglement, as well as secondary forces, including van der Waals, dipole-dipole, hydrophobic interactions and hydrogen bonding [10,11]. Since the interactions by which physical gelation occur do not comprise covalent cross-linking but mainly chain entanglement, an internal fluidity is observed in the network system, allowing for its reversible properties [12]. This may also attribute to creep flow when exposed to an external force for a long duration. Creep flow can be undesirable, depending on the particular applications to which the gel is designed. For





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