Thermoresponsive Hydrogels for Posterior Segment Drug Delivery

These materials appear to be promising for sustained release of drugs, including anti-VEGF agents, to the posterior segment.

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Thermoresponsive hydrogels have been proposed for a number of biomedical uses, including encapsulation of therapeutic agents for sustained delivery.[1] These materials change from a solution to a gel in response to temperature change without any additional external stimulus. Generally, the hydrogels proposed for use in biomedical applications are liquid at ambient temperatures and gel at body temperature. This allows them to be injected through a needle or cannula and then to retain a therapeutic agent in a gel state and release it over time.

Potential applications for thermoresponsive hydrogels in the eye include delivery of drugs to the posterior segment. Currently, the most efficient method for posterior segment drug delivery is intravitreal injection. However, this is also a highly invasive method, with numerous potential complications, including endophthalmitis, retinal tears and detachments, and cataract formation. This method is also limited to bolus drug delivery and does not allow extended or sustained release of the therapeutic agent.

Despite these limitations, intravitreal injection of therapeutic agents for retinal disorders has become common in recent years, particularly since the introduction of vascular endothelial growth factor (VEGF) inhibitors for the treatment of choroidal neovascularization in age-related macular degeneration. The anti-VEGF drugs approved for use in the United States are labeled for frequent use, at either 4- or 6-week intervals.[2,3] It has been proposed that thermoresponsive hydrogels might be used to deliver these large molecules efficiently to the posterior segment, with sustained release over time to potentially decrease the frequency of treatments.

POTENTIAL FOR POLYMERS

Polymers have the ability to swell in water or in an aqueous solvent system and to hold materials or drugs, especially when in a cross-linked format. Through the manipulation of their permeation and diffusion characteristics, hydrogels can be made to retain both hydrophobic and hydrophilic agents, small molecules and macromolecules. In addition, as noted above, they can be made temperature sensitive.

Figure 1. PNIPAAm is a thermoresponsive hydrogel. At room temperature it is a hydrated polymer that is hydrophilic in nature. With increase in temperature it collapses into a gel and becomes hydrophobic.

For a thermoresponsive polymer to act as an effective vehicle for drug delivery, it would have to meet a number of criteria. It would need to be capable of delivery via a relatively noninvasive method, such as a small-gauge needle, into the juxtascleral space or into the vitreous cavity. It would also have to be capable of sustained release of its cargo drug for at least 3 to 6 months in order to provide significant advantage over current delivery methods. It would have to be highly efficient at encapsulating an anti-VEGF agent. And it would have to be nontoxic and easy to manufacture, store, and use.

Poly(N-isopropylacrylamide) (PNIPAAm) is one of the natural polymers that exhibits thermoresponsive characteristics.[4] At room temperature it is a hydrated polymer that is

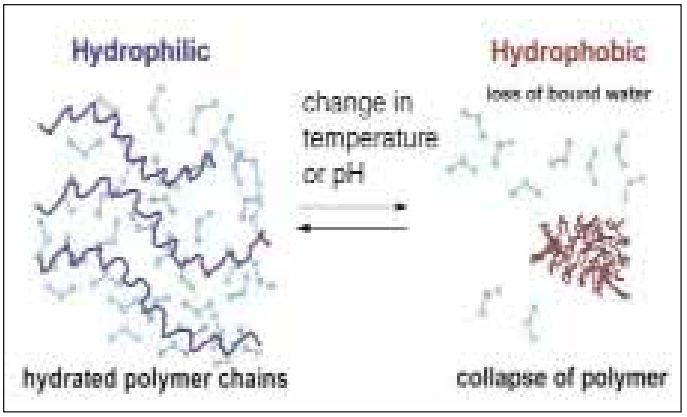

Figure 2. Poly(N-isopropylacrylamide), (PNIPAAm), has thermosensitive swelling characteristics.

hydrophilic in nature. With increase in temperature it collapses into a gel and becomes hydrophobic (Figure 1). This phase change can occur rapidly in response to temperature change, in some cases within a minute.

In order to be able to control the release of the anti-VEGF agent, the PNIPAAm was cross-linked with another polymer, poly(ethylene glycol) diacrylate (PEG-DA). This allows control of the diffusion rate through regulation of the pore size of the polymer system. Addition of PEG-DA does not greatly change the thermoresponsive nature of the PNIPAAm. The lower critical solution temperature (LCST) was shifted approximately 1°C.

PROTEIN RELEASE STUDY

In order to assess the potential of this thermoresponsive hydrogel as a drug-delivery platform, we studied its protein-release characteristics and subsequently measured the bioactivity of released proteins.[5,6]

Thermoresponsive hydrogels were synthesized using PNIPAAm cross-linked with PEG-DA. Bovine serum albumin (BSA), and immunoglobulin G (IgG) were encapsulated into the hydrogels. With a molecular weight of 66 kDa, BSA is comparable in size to the anti-VEGF drug ranibizumab. IgG has a molecular weight of 150 kDa, comparable to bevacizumab. The protein cargoes were encapsulated in hydrogels with a variety of pore sizes, as determined by the density of cross-linking, and the effect of cross-linker density on protein release was measured at several time points.

The cross-linked hydrogel demonstrated fast, reversible phase change following temperature alteration. As the concentration of PEG-DA increased, its viscous and elastic modulus properties also increased, prolonging protein release. In hydrogels with lower cross-linker density, and therefore with larger pores, protein release was faster. These lower-density gels were also more pliable, suggesting that injection through a 27-gauge needle for intravitreal delivery would be more feasible. Release profiles were similar for BSA and IgG, with slower release for more tightly cross-linked PEG-DA.

There was an early burst of release in the first 24 hours, followed by the achievement of a steady state that was sustained for at least 3 weeks. Examination of the gels after the experiment showed that a significant amount of entrapped protein remained.

The bioactivity of released proteins was also assessed. Bevacizumab was encapsulated in the thermoresponsive polymer as described above and released from the gel after 1 hour and 24 hours via temperature change. Human umbilical vein endothelial cells were stimulated with VEGF and inhibited with the released bevacizumab. The released proteins were found to be biologically active.

CONCLUSIONS

Recently developed thermoresponsive hydrogels can encapsulate and release proteins, including currently used anti-VEGF agents. Bevacizumab released by the thermoresponsive hydrogel is bioactive.

Future work will include modification of the current gel formulation to extend the release time and to make it fully biodegradable.

Thermoresponsive hydrogels appear to be a promising, minimally invasive platform for sustained delivery of drugs in the posterior segment. ■

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