Executive Summary

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Project „Self-heating hydrogel for mechanically-controlled drug release"

The primary objective of this project is to utilize the "lost" dissipation resulting in a temperature increase to locally trigger and/or accelerate the release of the drug or growth factor incorporated in a hydrogel along with obtaining temporal control of this release. By taking advantage of dissipation properties of hydrogels, we can provide a delay between initiation of mechanical load and release of the drug. This delivery method would be particularly beneficial for the release of growth factor, as it has been shown that cell receptor to growth factor is activated 5 to 20 min following a mechanical loading.

After the estimation of required dissipation energy via a finite element model of heat transfer in knee cartilage, we calculated the dissipation of poly(2-hydroxyethyl methacrylate), or PHEMA-,based hydrogels and optimized them to reach the required conditions. Our optimized structure is PHEMA-based hydrogels crosslinked with EGDMA.
Temperature-sensitive nanogels based on poly(N-isopropyl acrylamide) (PNIPAm) are good candidates for the proposed application however the studies are in progress on tuning the response temperature (via copolymerization with other monomers like HPMA) and release itself. Optimal conditions for crosslink density are yet to be achieved, and at this point either the release from nanogels happens as a consequence of diffusion, or no release is observed due to the drug entrapment into small meshes of microgel. Also, the previously proposed model of the responsive particle with a peptide crosslink is being explored, and there are some promising results obtained on a system with simpler (non-temperature sensitive) peptide pair.
To explore the feasibility of using dissipative properties to control delivery from thermosensitive polymer-based systems, we developed a unique hydrogel system consisting of two components: i) PHEMA-based highly dissipative hydrogel matrix and ii) PNIPAM-based thermosensitive nanoparticles, which are incorporated in hydrogel during hydrogel formation. The nanoparticles shrink (from 340 nm to 250 nm between 36°C and 37°C) when temperature passes their lower critical solution temperature (LCST) due to temperature increase induced by viscous dissipation following mechanical loading. Following shrinkage of nanoparticles, the corresponding permeability of the hydrogel increases and facilitates the release of its payload. We studied the drug release of such a system in a heat isolated system. We showed that the temperature of hydrogels can increase more than 1°C after 5 min loading in this set up (1.5 Hz, 15% deformation).
Under mechanical loading, when environmental temperature was fixed to 36°C, a statistically significant increase (133%) in Xylene Cyanole FF release was observed between the 5 and 8 min loading demonstrating the delayed release of the dye following a mechanical loading. Repeating the experiment at the initial temperature fixed to 34°C (where the temperature of hydrogels stays below LCST under load) showed no significant difference in Xylene release between 5 or 8 min loading.
The most probable effect, which can explain the results is the temperature-induced shrinkage of nanoparticles due to the dissipation properties of the hydrogel that changed the permeability of the hydrogel. This was then experimentally confirmed.