

Enzyme Responsive Polymer Hydrogel Particles

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Enzymes, and specifically proteases, play essential roles in biochemical processes. Indeed, specific proteolytic enzymes have been identified to play key roles in disease states and are therefore valuable targets for therapeutic programs [1]. We will describe a conceptually new approach to polymer-based enzyme-triggered release whereby the selective catalytic action of (disease specific) enzymes triggers a charge-induced swelling response in chemically cross-linked hydrogel particles, resulting in the release of physically entrapped macromolecules [2]. This approach has a number of advantages over existing methods: it does not require covalent modification of the drug molecules, thus chemical requirements upon the drug molecules are more flexible. The polymer material itself does not disintegrate upon release, and release rates will no longer be governed directly by enzyme kinetics. PEG-based cross-linked polymers were modified with peptide linkers that have a dual function: sensing and actuation. The sensing part consists of enzyme cleavable linker (ECL) and the actuation part consists of two oppositely charged amino acids that flank the ECL on either side, thus creating a zwitterionic peptide that confers no overall charge when coupled to a hydrogel. Upon selective enzyme hydrolysis of the ECL, a doubly negatively charged carboxylic acid fragment is removed, leaving a doubly cationic amine fragment tethered to the polymer, thus placing an overall positive charge on the gel and causing it to swell and release a payload.

Two-photon microscopy was used to show the release of the dextran from the Ala-Ala ECL incubated with thermolysin by a time-lapse experiment (fig 1). Release is only observed if the peptide-modified hydrogel is incubated with an enzyme capable of cleaving the ECL.

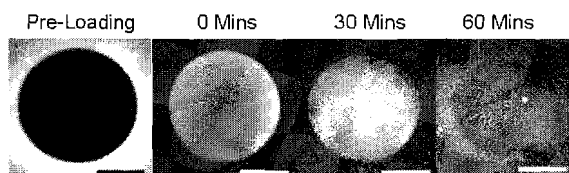


Figure 1: Complete release of the dextran from the Ala-Ala ECL is observed after 60 mins

Further work includes tailoring the peptide linker for the optimum release of oppositely charged protein molecules, offering both quick and slow release mechanisms.

References

- (1) Thornton, P. D. McConnell G. and Ulijn, R. V. *Chem. Commun.* **2005**, 47, 5913-5915.
- (2) Thornton, P. D. Mart, R. J. and Ulijn, R. V. *Adv. Mater.* **2007**, 19, 1252-1256.