Hydrogels with controlled properties for releasing pharmacologically active compounds

PhD. Student Emilian GHIBU

PhD. Advisor Prof. Raluca STAN

Abstract

This thesis demonstrates the broad potential of poly(2-isopropenyl-2-oxazoline) (PiPOx) based crosslinked materials as multifunctional systems for controlled drug delivery and antifouling applications in both hydrogels and nanofibers. Despite PiPOx's versatility, its biomedical applications, particularly degradable hydrogels for drug delivery and biohybrid nanofibers, have been largely unexplored. This work addresses these gaps by demonstrating how PiPOx properties can be rationally tailored for specific biomedical needs.

Biodegradable PiPOx hydrogels were synthesized under mild, aqueous conditions using bio-based dicarboxylic acids as crosslinkers. Crosslinker chemistry strongly affected stability, degradation, and drug-release behavior. The hydrogels exhibited hydrolytic and enzymatic degradability, tunable mechanical and swelling properties, and controlled drug release under simulated physiological conditions, confirming their suitability for targeted delivery.

The versatility of PiPOx hydrogels was further evidenced by their capacity to load and release diverse therapeutic agents, including anticancer, anti-inflammatory, and antimicrobial drugs, as well as nucleic acids. This ability arises from multiple non-covalent interactions between PiPOx and drug molecules, coupled with pH-responsive behavior of the 2-oxazoline rings, which enabled precise control and sustained release profiles.

In addition to drug delivery, thermal analyses revealed enhanced thermal stability upon crosslinking and the existence of water inside the hydrogels predominantly in the non-freezing water state. Biological assays demonstrated low cytotoxicity, minimal inflammatory response, and promising hemocompatibility of PiPOx hydrogels. Importantly, PiPOx hydrogels resisted protein adsorption and platelet adhesion, underscoring their antifouling potential for blood-contacting devices.

Biohybrid nanofibers were also fabricated via a green electrospinning process from aqueous solutions of PiPOx and fish gelatin. This method promoted "on-the-fly" crosslinking of PiPOx by the carboxyl groups of gelatin, while additional stabilization crosslinking was achieved post-electrospinning by crosslinking gelatin with glutaraldehyde or PiPOx with malic acid, thereby enhancing the aqueous and thermal stability of the nanofibers. The resulting nanofibers maintained nanoscale morphology and exhibited superior cell-interactive properties compared to gelatin, making them attractive for wound-healing applications.

Overall, this work expands the scope of PiPOx-based biomaterials, establishing PiPOx as a promising platform for controlled drug delivery, antifouling surfaces, and regenerative medicine.