

# Poly(2-oxazoline)s: From an attractive alternative to PEG to an exotic speciality and back?

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Already in the earliest days of research into PEGylation, Poly(2-oxazoline)s (POx) have been investigated and established as attractive and efficient alternatives to PEG [1], but while PEG rapidly became the gold standard for hydrophilic biomedical polymers and PEGylation is one of the best known concepts in (bio)pharmaceutical technology, POx have long been living in relative obscurity, with all but a handful of researchers world-wide working with them.

Even though research around POx became more lively again in the late 2000s, the recent decade has been particularly interesting. Apart from drug [2,3], protein [4] and gene delivery systems [5], POx based thermoresponsive hydrogels have been developed for bioprinting. POx-based thermogels show interesting structure-property relationships [6][7][8] and rheological properties particularly suited for bioprinting, all in combination with excellent cytocompatibility.

This contribution will revisit the development of POx-based hydrogels for drug delivery and 3D printing, with a focus on biofabrication.

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## **References**

- [1] Zalipsky, S.; Hansen, C.B.; Oaks, J.M.; Allen, T.M., 1996. Evaluation of Blood Clearance Rates and Biodistribution of Poly(2-oxazoline)-Grafted Liposomes. *J. Pharm. Sci.* **1996**, *85*, 133–137.
- [2] Luxenhofer, R.; Schulz, A.; Roques, C.; Li, S.; Bronich, T.K.; Batrakova, E.V.; Jordan, R.; Kabanov, A.V. Doubly amphiphilic poly (2-oxazoline) s as high-capacity delivery systems for hydrophobic drugs. *Biomaterials* **2010**, *31*, 4972–4979.
- [3] Kierstead, P.H.; Okochi, H.; Venditto, V.J.; Chuong, T.C.; Kivimae, S.; Fréchet, J.M.J.; Szoka, F.C. The effect of polymer backbone chemistry on the induction of the accelerated blood clearance in polymer modified liposomes. *J. Control. Release* **2015**, *213*, 1–9.
- [4] Tong, J.; Luxenhofer, R.; Yi, X.; Jordan, R.; Kabanov, A.V. Protein Modification with Amphiphilic Block Copoly(2-oxazoline)s as a New Platform for Enhanced Cellular Delivery. *Mol. Pharmaceutics* **2010**, *7*, 984–992.
- [5] Sanchez, A.J.D.S.; Loughrey, D.; Echeverri, E.S.; Huayamates, S.G.; Radmand, A.; Paunovska, K.; Hatit, M.; Tiegreen, K.E.; Santangelo, P.J.; Dahlman, J.E. Substituting Poly(ethylene glycol) Lipids with Poly(2-ethyl-2-oxazoline) Lipids Improves Lipid Nanoparticle Repeat Dosing. *Adv Healthcare Mat.* **2024**, *13*, 2304033.
- [6] Hahn, L.; Karakaya, E.; Zorn, T.; Sochor, B.; Maier, M.; Stahlhut, P.; Forster, S.; Fischer, K.; Seiffert, S.; Pöppler, A.-C.; Detsch, R.; Luxenhofer, R., An Inverse Thermogelling Bioink Based on an ABA-Type Poly(2-oxazoline) Amphiphile. *Biomacromolecules* **2021**, *22*, 3017–3027
- [7] Hahn, L.; Keßler, L.; Polzin, L.; Fritze, L.; Forster, S.; Helten, H.; Luxenhofer, R. ABA Type Amphiphiles with Poly(2-benzhydryl-2-oxazine) Moieties: Synthesis, Characterization and Inverse Thermogelation. *Macro Chem. Phys.* **2021**, *222*, 2100114
- [8] Hahn, L.; Zorn, T.; Kehrein, J.; Kielholz, T.; Ziegler, A.-L.; Forster, S.; Sochor, B.; Lisitsyna, E.S.; Durandin, N.A.; Laaksonen, T.; Aseyev, V.; Sotriffer, C.; Saalwächter, K.; Windbergs, M.; Pöppler, A.-C.; Luxenhofer, R. Unraveling an Alternative Mechanism in Polymer Self-Assemblies: An Order–Order Transition with Unusual Molecular Interactions between Hydrophilic and Hydrophobic Polymer Blocks. *ACS Nano* **2023**, *17*, 6932–6942.