The crosstalk between DOSY NMR and neutron spin echo spectroscopy: what can we learn about the chain dynamics of block and gradient poly(copoly-2-oxazoline) micelles and relative unimer population?

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Although gradient copolymers have been known for almost 50 years, there is a lack of detailed knowledge of corona chain mobility in polymeric micelles and how this is different from the chain mobility of block copolymer micelles. This knowledge could be very useful, especially for polymers that are highly potent for drug encapsulation due to the strong correlation between internal dynamics and loading and release efficacy. This holds true for poly(2-alkyl-2-oxazoline)s, considering the superior biocompatibility of poly(2-methyl-2-oxazoline) and poly-(2-ethyl-2-oxazoline) in comparison with classical polyethylene glycol [1]. Here, we report on a comprehensive study of the chain dynamics of copolymer micelles composed of amphiphilic poly(2-methyl-2-oxazoline)- *grad* -poly(2-phenyl-2-oxazoline) gradient copolymers in comparison to their block copolymer analogues. Apart from the chain dynamics, we also focused on the presence of unimers, single polymer chains that coexist in solution with the polymer micelles. It is expected that gradient copolymers should have a higher number of unimers than their block copolymer analogues, as they commonly have a higher critical micellization concentration. We varied the hydrophobic/hydrophilic balance and water/ethanol ratios to understand their impact on chain dynamics and unimer-micelle equilibrium. The results highlight the clear impact of the polymer monomer distribution on the shell polymer chain dynamics. Neutron spin echo (NSE) and diffusion ordered spectroscopy (DOSY NMR) experiments evidenced that the polymer chains in a micellar hydrophilic shell composed of gradient copolymers have additional slow motion, making it distinct from their block copolymer analogues [2]. The existence of such an additional chain dynamic could be explained by several plausible theories, including rotational diffusion, Zimm dynamics, or their combination. In addition, we were able to extract the relative populations of unimers and micelles in solutions of both gradient and block copolymers, and our results provided direct proof that the equilibrium between micelles and unimers is indeed shifted to more unimers for gradient copolymers, probably due to lower interphase tension. The reported findings contribute to the understanding of polymer dynamics in polymeric micelles and provide valuable insights for the design of functional polymer-based materials.

Keywords:
poly(2-alkyl-2-oxazoline), poly(2-methyl-2-oxazoline), polyoxazoline, NSE, DOSY, polymer dynamics, unimer, micelle, drug delivery, gradient copolymer

References:

[1] Robert Luxenhofer, Anita Schulz, C. Roques, S. Li, Tatiana K. Bronich, Elena V. Batrakova, Rainer Jordan, Alexander V. Kabanov, Biomaterials, 31, 4972-4979, 2010
[2] Anastasiia Murmiliuk, Olaf Holderer, Zdenek Tosner, Bart Verbraeken, Ondrej Sedlacek, Richard Hoogenboom, Sergey K. Filippov, submitted to the Journal of Colloid and Interface Science, 2026

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