Photoactivated Modulation of Lipid Nanosystems: A Structural and Kinetic Study

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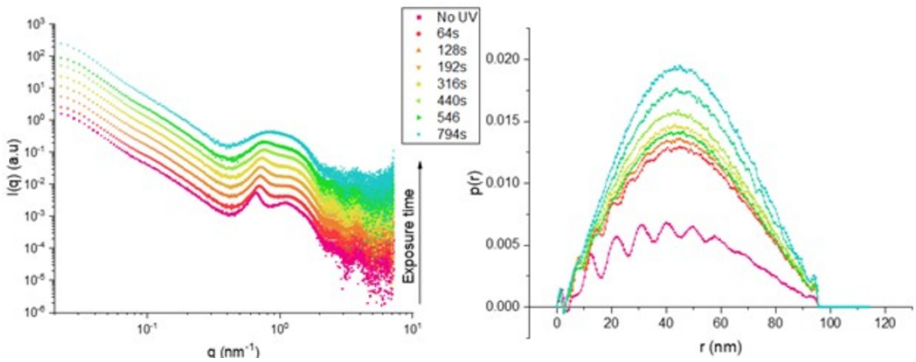
Functionalized lipid nanocarriers with precisely tunable light-responsiveness represent a promising route to overcome the intrinsic limitations of conventional PEGylated systems, such as poor targeting efficiency and hindered interactions with biological membranes—the so-called PEG dilemma. While PEG functionalization provides stealth properties and enhanced circulation time, it can also suppress endocytic uptake and membrane fusion. To address this challenge, we developed and characterized photoresponsive lipid-based nanocarriers capable of controlled PEG removal and reversible structural modulation under light irradiation. Two complementary strategies were explored: (i) the incorporation of stimuli-responsive PEGylated amphiphiles that undergo selective photocleavage under monochromatic near-UV light, and (ii) the embedding of azobenzene-based molecular switches within the lipid bilayer to induce reversible trans–cis isomerization. Upon near-UV (365 nm) irradiation, PEG shedding and photoisomerization processes were triggered in situ during Time-Resolved Small Angle X-ray Scattering (TR-SAXS) experiments, enabling direct observation of structural transitions at millisecond timescales. UV–visible and fluorescence spectroscopies complemented these measurements to monitor kinetic profiles and confirm the efficiency of light-triggered transformations. Photoresponsive ethosomal nanocarriers were prepared via microfluidic synthesis and featured three distinct azobenzene-based amphiphiles intercalated in the bilayer. The reversible photoisomerization of these switches altered bilayer geometry, packing, and permeability, leading to light-controlled modulation of membrane structure and, in some cases, transient pore formation. Depending on the molecular design, structural rearrangements were found to be fully or partially reversible upon white-light irradiation. Overall, our work elucidates the kinetic and structural dynamics underlying light-induced PEG cleavage and azobenzene-driven bilayer remodeling in lipid nanocarriers. These insights pave the way for the rational design of next-generation stimuli-responsive nanosystems capable of on-demand drug release and fine-tuned control over nanocarrier functionality.

Keywords:
light-triggered structural modifications, lipid nanoparticles, azo-lipids, photo-lipids, azobenzene-based amphiphiles, Tr-SAXS



Scattering profiles of photoactivated PEG cleavage (left) and corresponding pair distribution functions (right)

References:

Zonglin Chu, Yanxiao Han, Tong Bian, Soumen De, Petr Král, Rafal Klajn. *JACS* **2019.**
Wonmin Choi, Claudia Battistella, Nathan C. Gianneschi. *Biomater. Sci* . **2021.**
Mahmoudreza Doroudgar, Johannes Morstein, Johanna Becker-Baldus, Dirk Trauner, Clemens Glaubitz. *JACS* **2021.**