

POLY(N-METHYL VINYLACETAMIDE)-LIPID CONJUGATES: NEW PEG ALTERNATIVES FOR THE SURFACE MODIFICATION OF LIPIDIC NANOVECTORS DEDICATED TO GENE THERAPY

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Surface modification of lipid carriers via PEGylation prevents particle aggregation and imparts "stealth" properties, enhancing their circulation time in the bloodstream. However, PEGylation presents several limitations, including the ABC (accelerated blood clearance) effect, which leads to rapid elimination of the drug upon repeated administration, hypersensitivity reactions, and the so-called "PEG dilemma" which limits the cellular uptake and endosomal escape. Recent studies emphasized the benefits of using poly(*N*-methyl vinylacetamide) (PNMVA) as alternative to PEG for developing non-toxic, efficient, and less immunogenic lipid-based carriers, in particular siRNA-loaded lipid nanoparticles.¹⁻³ This communication will present the precision synthesis of a series of lipid-poly(*N*-methyl vinylacetamide) conjugates by reversible addition-fragmentation chain transfer (RAFT) polymerization and explore their potential for decorating lipid nanocarriers. The lipid structure and polymerization degree of PNMVA were varied to assess the impact of these parameters on the interaction of the lipid-PNMVA conjugates with lipid bilayers and on the structure and surface properties of the resulting lipid nanocarriers.

¹ Berger M.; Toussaint F.; Djemaa S. Ben; Laloy J.; Pendeville H.; Evrard B.; Jérôme C.; Lechanteur A.; Mottet D.; Debuigne A.; Piel G. J. *Control. Release* 2023, 361, 87–101. DOI :10.1016/j.jconrel.2023.07.031.

² Berger M.; Toussaint F.; Ben Djemaa S.; Maquoi E.; Pendeville H.; Evrard B.; Jérôme C.; Leblond Chain J.; Lechanteur A.; Mottet D.*; Debuigne A.*, Piel G.* *Adv Healthc Mater.* 2024, 13(8), 2302712. DOI: 10.1002/adhm.202302712.

³ Debuigne A.; Piel G., Mottet D.; Toussaint F.; Berger M.; Bendjema S.; Lechanteur A. *Polymer Derivatives and their use as lipid nanoparticle modifiers.* Patent 2024, WO2024227713A1 & EP4458870A1.

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