Bioinspired lipoprotein-mimetic nanocarriers: Tackling drug solubility and permeability challenges

Fabian Klos[1], Christopher Haußß[1], Stefanie Gier[1], Maike Windbergs[1]

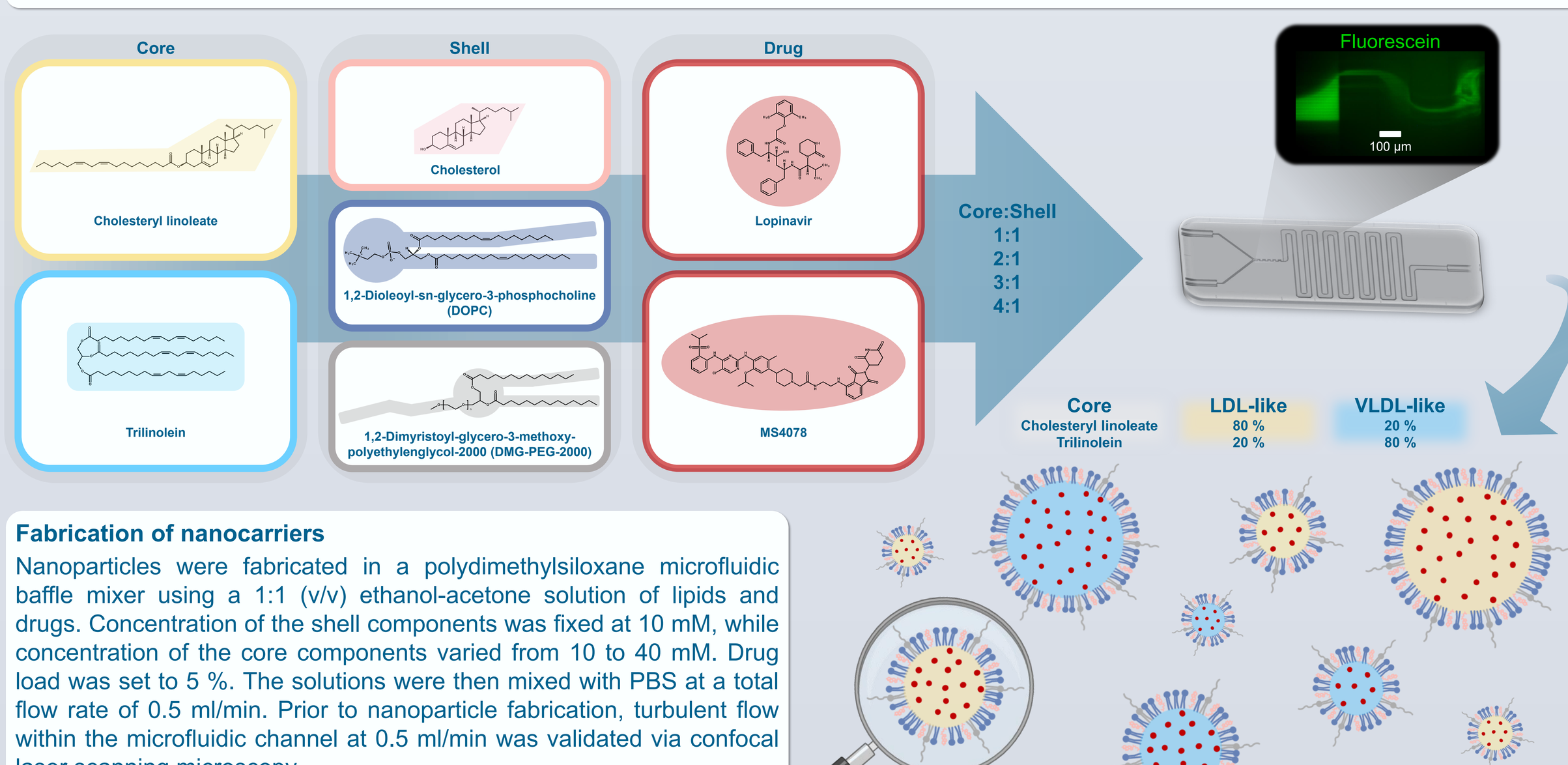
[1]Goethe University Frankfurt, Institute of Pharmaceutical Technology, Max-von-Laue Straße 9, Frankfurt am Main, Germany
✉ Klos@em.uni-frankfurt.de

GOETHE UNIVERSITÄT FRANKFURT AM MAIN

Visit us online!

Introduction

The growing prevalence of poorly soluble and permeable chemical entities, including new drug classes such as proteolysis targeting chimeras (PROTACs), necessitates innovative delivery strategies, overcoming the limitations of conventional formulations. Natural lipoproteins, integral in lipid metabolism, possess a distinctive core-shell architecture with a lipophilic inner phase, providing an ideal platform for encapsulating such poorly bioavailable drugs. Due to their biocompatibility and capacity for functionalization, lipoprotein-mimetic nanocarriers not only enhance drug solubility but also facilitate targeted delivery by improving cellular recognition. Using these lipoprotein structures as a blueprint, we developed LDL- and VLDL-like nanocarriers with different core-shell ratios and evaluated their ability to incorporate the two BCS class IV drugs Lopinavir and MS4078.

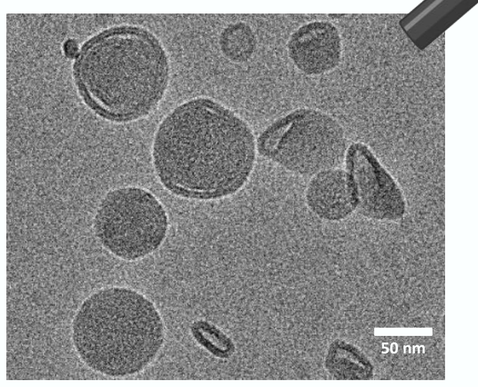


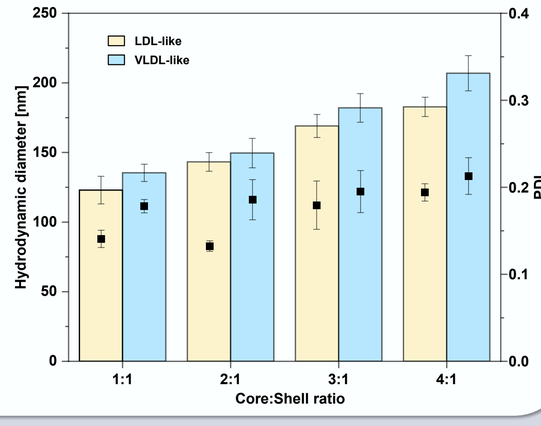
Fabrication of nanocarriers

Nanoparticles were fabricated in a polydimethylsiloxane microfluidic baffle mixer using a 1:1 (v/v) ethanol-acetone solution of lipids and drugs. Concentration of the shell components was fixed at 10 mM, while concentration of the core components varied from 10 to 40 mM. Drug load was set to 5 %. The solutions were then mixed with PBS at a total flow rate of 0.5 ml/min. Prior to nanoparticle fabrication, turbulent flow within the microfluidic channel at 0.5 ml/min was validated via confocal laser scanning microscopy.

Hydrodynamic diameter and polydispersity

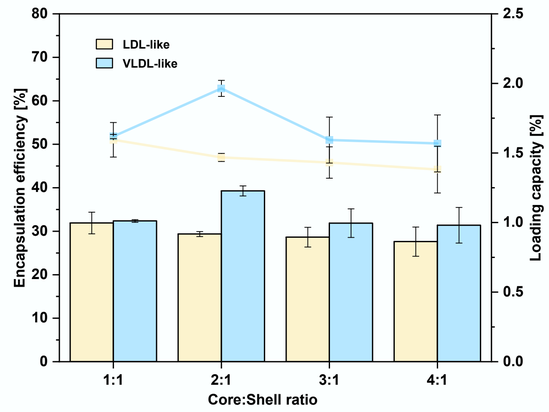
All lipid formulations encapsulating Lopinavir demonstrated an adequate hydrodynamic diameter and a narrow size distribution, measured by DLS. Increasing the core proportion resulted in a rise of the average particle size but had no significant effect on the PDI. The zeta potential measured by ELS was slightly negative for all compositions, with values reaching up to -2 mV. Cryo-TEM images showed the formation of a core-shell structure with emulsified triglycerides and cholesterol esters in the core. In addition, isolated liposomes and bleb-like structures were visible.





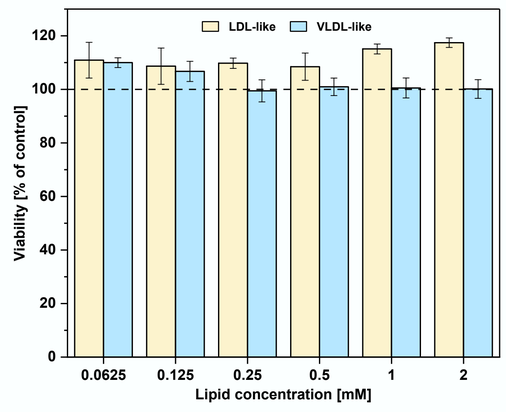
Drug encapsulation

Lopinavir encapsulation for all core-shell ratios was measured by HPLC after particle destruction. The VLDL-like compositions consistently exhibited a higher encapsulation compared to their LDL-like counterparts with loading capacities up to 2 %. Interestingly, both formulations demonstrated the highest encapsulation efficiency and loading capacity at a core-shell ratio resembling the biophysiological composition of lipoproteins.



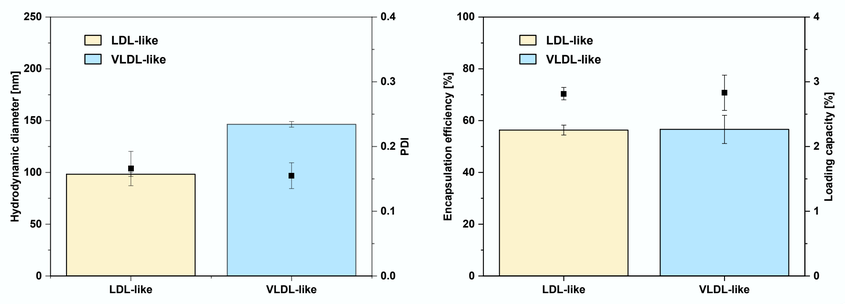
Biocompatibility

The biocompatibility of blank nanocarriers composed of the most promising VLDL-like (2:1) and LDL-like (1:1) core-shell ratios was assessed via MTT assay using human endothelial cells (hCMEC/d3). None of the two formulations caused any detrimental effects up to a total lipid concentration of 2 mM. Results were normalized to an untreated medium control.



Translation to PROTAC encapsulation

Finally, the best performing ratio for each particle type was loaded with 5 % MS4078. Resulting particles of both formulations exhibited physicochemical properties comparable to blank LDL-like and VLDL-like particles. However, encapsulation efficiency and loading capacity were prominently higher compared to Lopinavir-loaded particles, indicating favorable interactions between particle components and encapsulated model PROTAC.



Conclusions

- Lipoprotein-mimetic nanocarriers represent a promising platform for delivering drugs with challenging water solubility and permeability
- Core-shell ratios mimicking natural proportions yield the best results and are highly biocompatible

ACKNOWLEDGEMENTS
Studies and conference contribution were supported by the BMBF (PROXIDRUGS-BioDEL, 03ZU2109GA), and the Cluster project ENABLE funded by the Hessian Ministry for Science and the Arts.

Lipoid · Bundesministerium für Bildung und Forschung · PROXIDRUGS · EnABLE Ein Clusterprojekt des Landes Hessen