Influence of Small Molecules on Hydration-Induced Phase Distribution in Lipid Liquid Crystalline Depots

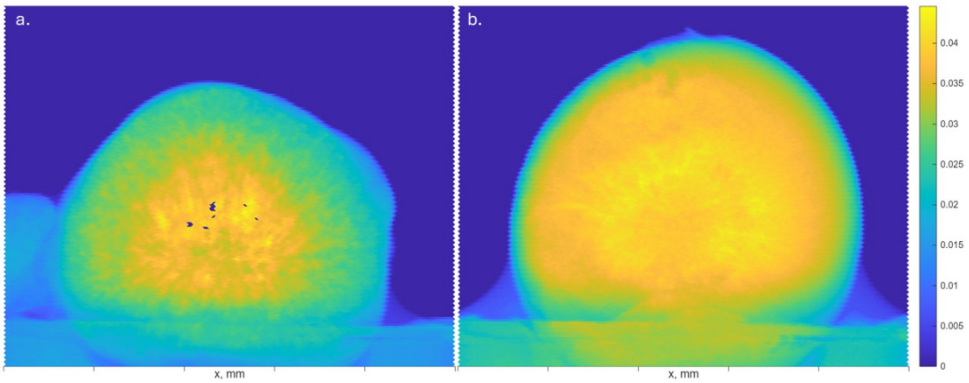
Jenni Engstedt [ab], Meruyert Turpanov [ab], Vitaly Kocherbitov [ab]

[a] *Biomedical Sciences, Faculty of health and Society, Malmö University, SE-205 06 Malmö, Sweden*
[b] *Biofilms – Research Center for Biointerfaces, Malmö University, SE-205 06 Malmö, Sweden*

jenni.engstedt@mau.se

Lipid liquid crystalline depots are formed through the self-assembly of amphiphilic lipids into liquid crystalline phases upon hydration and are widely used as biocompatible systems for sustained and controlled drug release. While previous work has highlighted the role of hydration-driven lipid redistribution and resulting spatial phase heterogeneity [1], the influence of lipid composition and additives on these processes remains less understood.
This study extends earlier findings by investigating how variations in lipid composition, additives and chemical environment affect phase distribution within lipid depots. Systems based on soybean and egg phosphatidylcholine, which differ in average fatty acid composition and exhibit distinct phase behavior during hydration, are combined with Span 80 and studied both in the absence and presence of additives such as ibuprofen, trimethylamine N-oxide, and urea. Advanced synchrotron SAXS is employed to resolve phase behavior within the depot across hydration times from 5 hours to 3 weeks, providing direct insight into structural organization and its temporal evolution.
The results show that both lipid composition and the presence of additives influence the phase distribution within the depots, with coexisting cubic and hexagonal structures forming distinct spatial arrangements. These findings highlight the sensitivity of lipid self-assembly to compositional and environmental factors, providing further insight into the mechanisms governing structure formation in lipid-based drug delivery systems and supporting continued efforts toward rational design of such systems.

Keywords:
Small angle x-ray scattering, Phase behavior, Liquid crystalline depots, Lipid-based drug delivery, Hydration-driven structural reorganization



Initial lipid composition and additives influence hydration kinetics and phase behavior. Comparison of a) SPC/Span 80 and b) EPC/Span 80 depots, both containing 2% TMAO, shows differences in cubic phase distribution after 3 days of hydration (2 mm spacing; intensity reflects cubic fraction).

References:

[1] Engstedt, J. *et al.* Hydration-induced lipid redistribution in swelling of controlled release liquid crystalline depots. *Commun Chem* **8** , 309 (2025). https://doi.org/10.1038/s42004-025-01739-0

Acknowledgements:

The authors acknowledge colleagues at the Water Science Lab at Malmö University and funding from the Sandberg Foundation. We also acknowledge the ForMAX beamline at MAX IV Laboratory and thank Kim Nygård and Mira Viljanen for their support.