**Investigation of thermodynamic phase transitions of lysolipid-containing thermosensitive liposomes by DSC and PPC**

Jessica Steigenberger¹,², Daniel Eckhardt¹, Michael Dunne², Brittany Epp-Ducharme³, Maximilian Regenold², Christine Allen², Heiko Heerklotz¹,²

¹Institute of Pharmaceutical Sciences, Albert-Ludwigs-University Freiburg, Baden-Württemberg, Germany
²Leslie Dan Faculty of Pharmacy, University of Toronto, Ontario, Canada

**Introduction:** Liposomes are commonly used as drug delivery vehicles, as drug encapsulation into them alters their pharmacokinetic and -dynamic properties. However, the necessary stability of liposomes often results in insufficient drug release once the target side is reached. This problem can be solved by an externally stimulated drug release from otherwise highly stable liposomes. Thermosensitive liposomes (TSL) are composed of a lipid mixture that is designed to undergo a thermodynamic phase transition at temperatures of mild hyperthermia (39 °C – 42 °C) and thereby trigger rapid drug release. Several TSL formulations, like the lysolipid-containing TSL (LTSL), have been developed and empirically optimized, but a detailed mechanistic and quantitative understanding as needed for a rational design and adjustment of formulation parameters is still lacking.

This work aims at a more thorough understanding of the molecular effect of lysolipids on TSLs and to evaluate whether and how the cargo affects the details of the thermodynamic phase transition of the LTSL carrier system.

**Methods:** The thermodynamic, including volumetric, effect of lysolipid on the phase behavior of multilamellar and unilamellar vesicles was studied by DSC, PPC, densitometry, and ITC. The effect of loading LTSL with alvespimycin, calcein, doxorubicin, or vinorelbine was checked by DSC.

**Results:** The data suggest the lysolipid to act by forming a eutectic with the membrane lipids at its content of 10 mol%, with a condensed complex being formed at higher lysolipid content. The drugs caused only minor shifts of transition temperature and width that require a moderate adaptation of a chosen TSL system for a specific cargo.

**Conclusion:** The results presented here on the phase behavior of lysolipid-lipid mixtures are in conflict with much of the previously established models and ideas. This work highlights the importance of utilizing proper model systems that can be understood by established thermodynamic models and phases and a cautious and critical application of this knowledge to the pharmaceutically relevant systems.

**References:**