

Thermodynamic and Structural effects of CaCl₂ on the Phase Transitions and Structures of Distearoyl-Phosphatidylcholine (DSPC) by Differential Scanning Calorimetry and X-Ray Diffraction

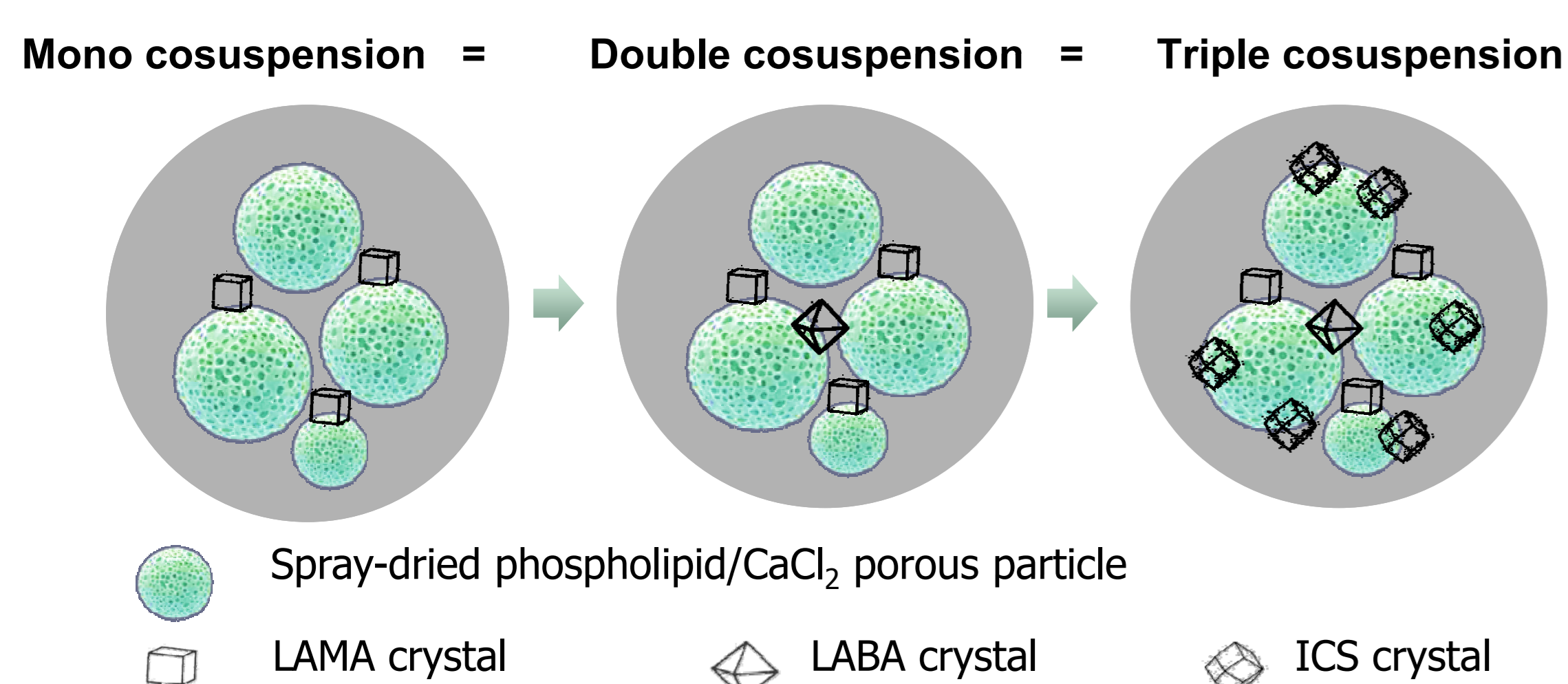
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Introduction

Phosphatidylcholines are well suited as excipients for respiratory drug delivery. To date, literature studies have focused on dipalmitoyl-phosphatidylcholine (DPPC) which has a lower T_m than DSPC. Spray-dried low density microparticles containing DSPC and CaCl₂ are used as a multi-functional excipient in the recently developed cosuspension pressurized metered dose inhalers (cpMDI).

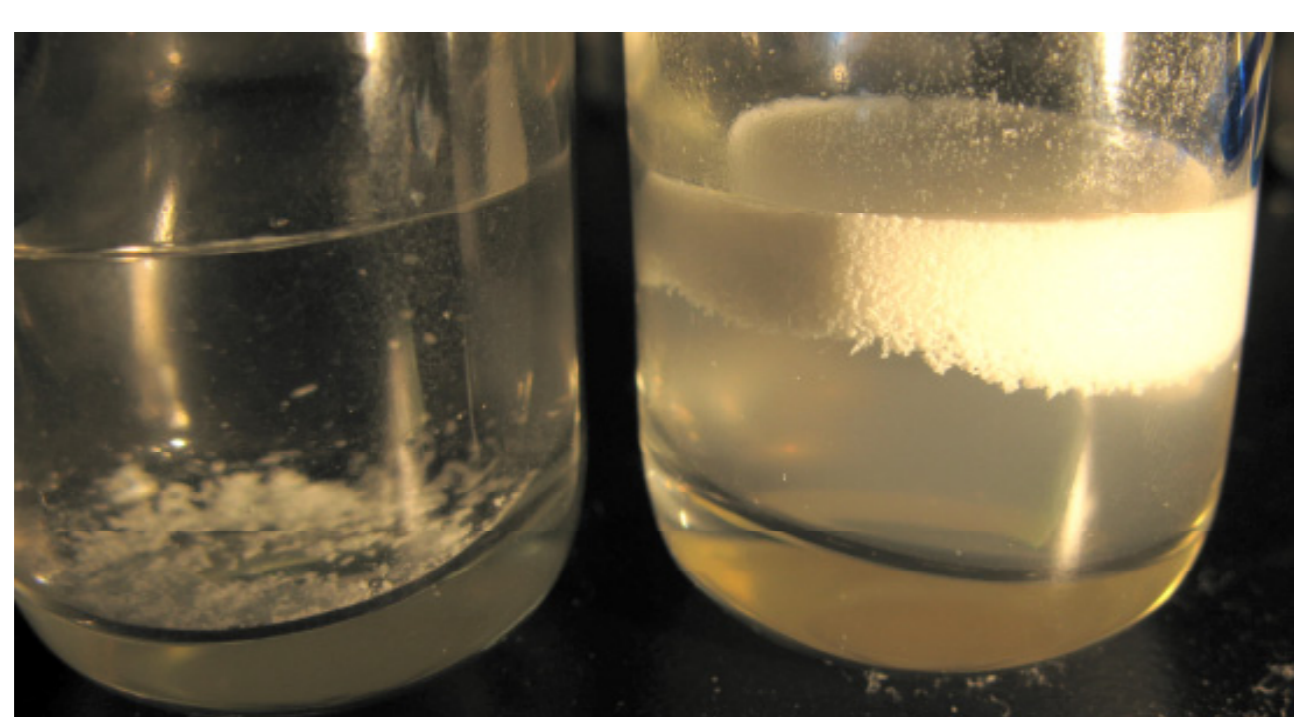
Phospholipid microparticles form uniform suspensions in hydrofluoroalkane (HFA) propellants and maintain their aerodynamic properties when actuated from the cpMDI. They can also be mixed with multiple micronized actives to prepare combination therapy pMDIs, which deliver each drug with remarkably similar aerodynamic properties independent of the number of drugs in the combination at the required dose.



Phospholipid microparticles contain DSPC and CaCl₂ in the ratio of 2:1 and improve the physical stability of micronized drug suspensions in HFA.

Phospholipid microparticles associate with API microcrystals to form a stable cosuspension

Micronized GP alone (left vial) and micronized GP cosuspension with phospholipid microparticles (right vial) demonstrating formation of drug-microparticle ensembles.



Objective

Addition of CaCl₂ to DSPC is known to improve its physical stability, but there has been limited research to elucidate the phase behavior as a function of temperature and hydration.

The objective of this study was to determine the phase diagram of DSPC / CaCl₂ at various hydration levels using thermal and structural analysis.

Materials and Methods

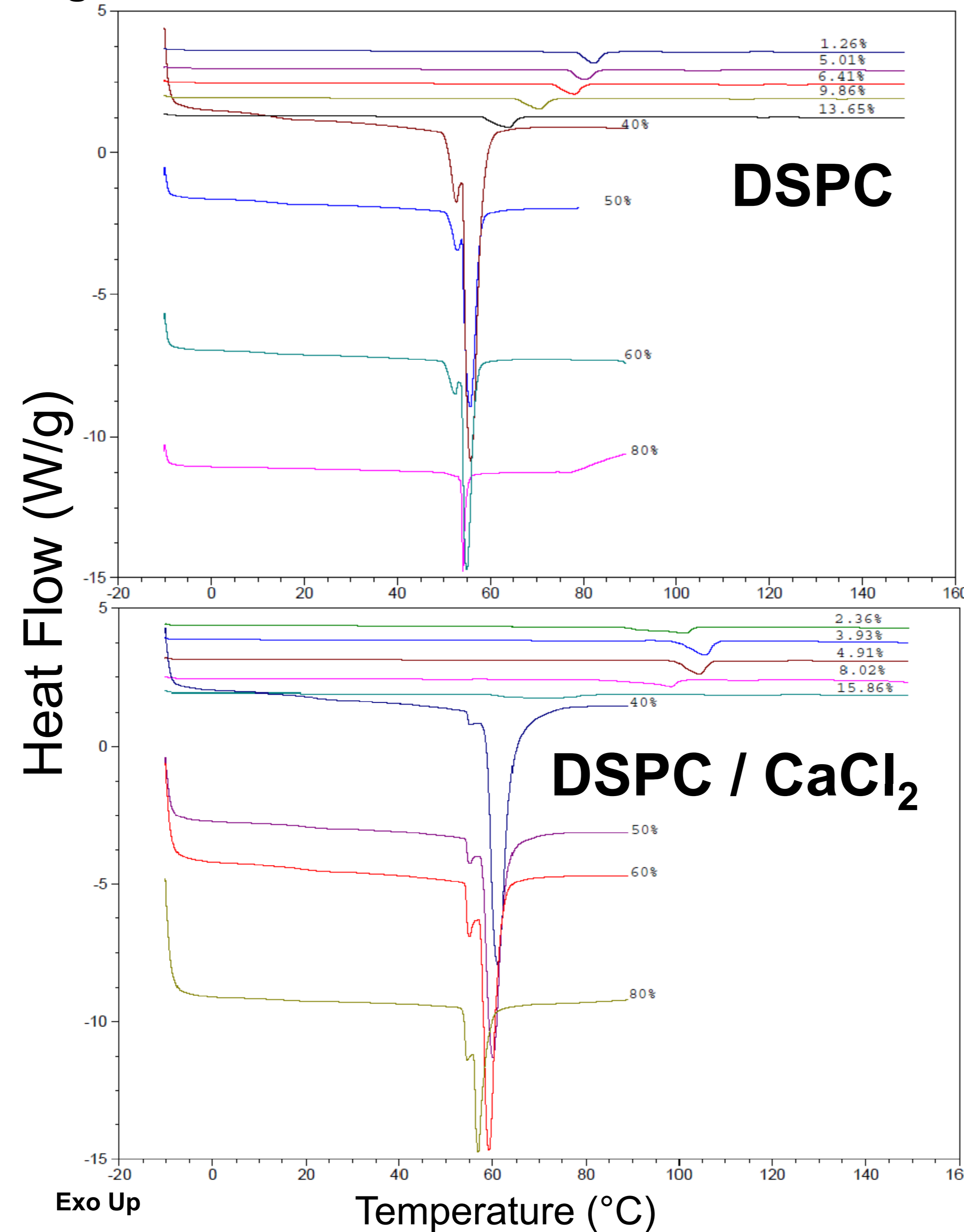
Aqueous dispersions of DSPC (Lipoid LLC) containing 20-80% water were prepared by sonication at 80°C. Samples containing <20% water were prepared by equilibrating samples at various relative humidities.

DSC curves were obtained from -10°C to 90 or 150°C using a scan rate of 2.5°C/min. XRPD patterns of selected samples were generated using transmission mode to capture low angle diffraction.

Results

DSPC phase transitions are consistent with DPPC transitions conveying a decrease in T_m with increasing %water.

Fig. 1: Effect of %Water on DSPC & DSPC / CaCl₂ T_m

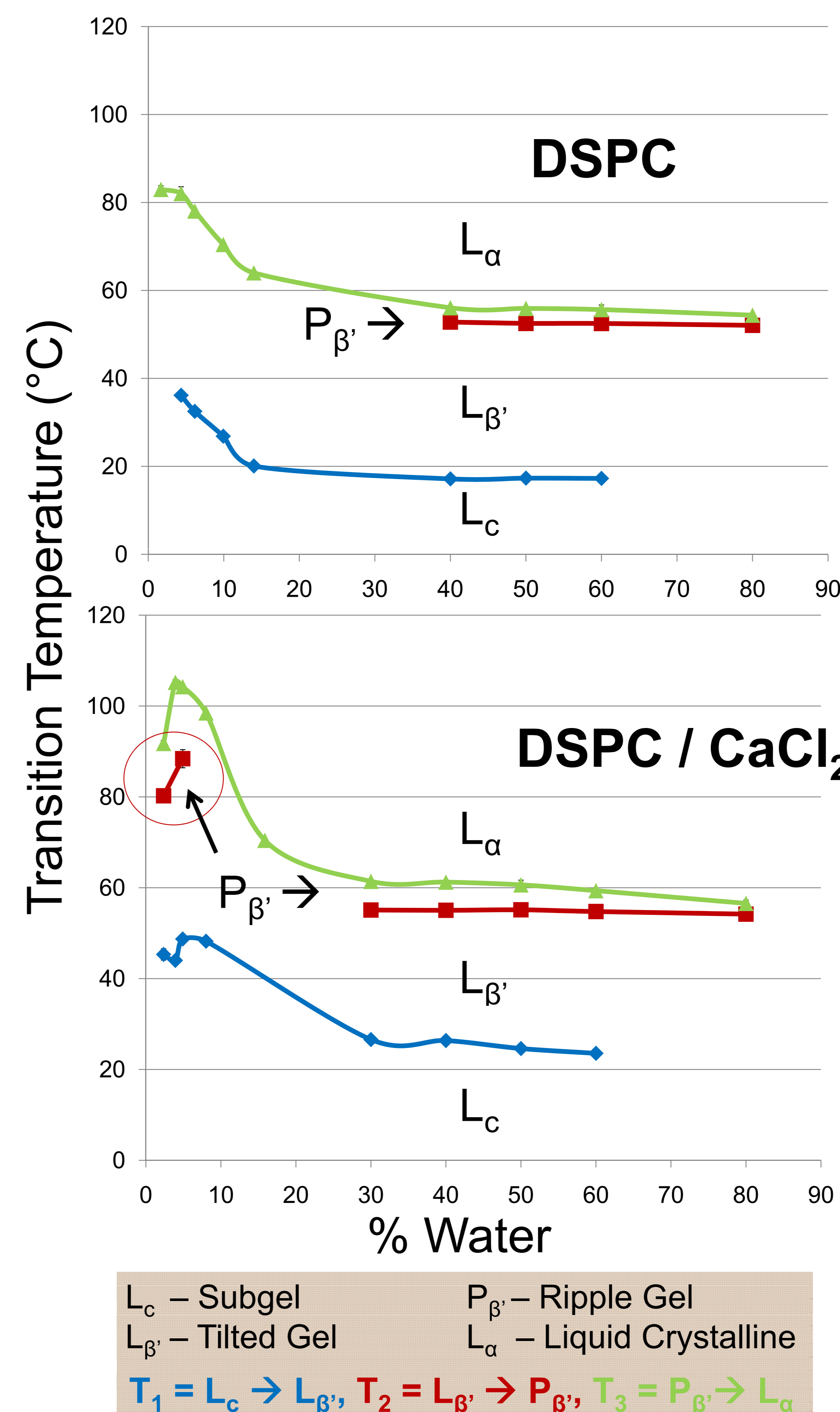


Addition of CaCl₂ leads to an increase in T_m of the phase transitions. At water contents >20% the transition temperature increase is minimal (avg. 3°C), but at low water content a substantial increase (avg. 20°C) is observed (Fig. 2)

This correlates with the extent of structural changes characterized by the CaCl₂ interactions with the phospholipid head group, promoting increased rigidity of the acyl chains leading to the stabilization of the ripple gel phase ($P_{\beta'}$) even at low water contents as evidenced by DSC (Fig. 2: red circle) and XRPD (Fig. 3).

Results

Fig 2: Phase Diagrams of DSPC & DSPC / CaCl₂



The symmetry of the diffraction peak at 21.4° in 2θ (Fig. 3) is indicative of hexagonal packing corresponding to $P_{\beta'}$ structures.

Fig 3: Ripple gel phase is stable at ambient conditions as suggested by XRPD of DSPC / CaCl₂ Microparticles

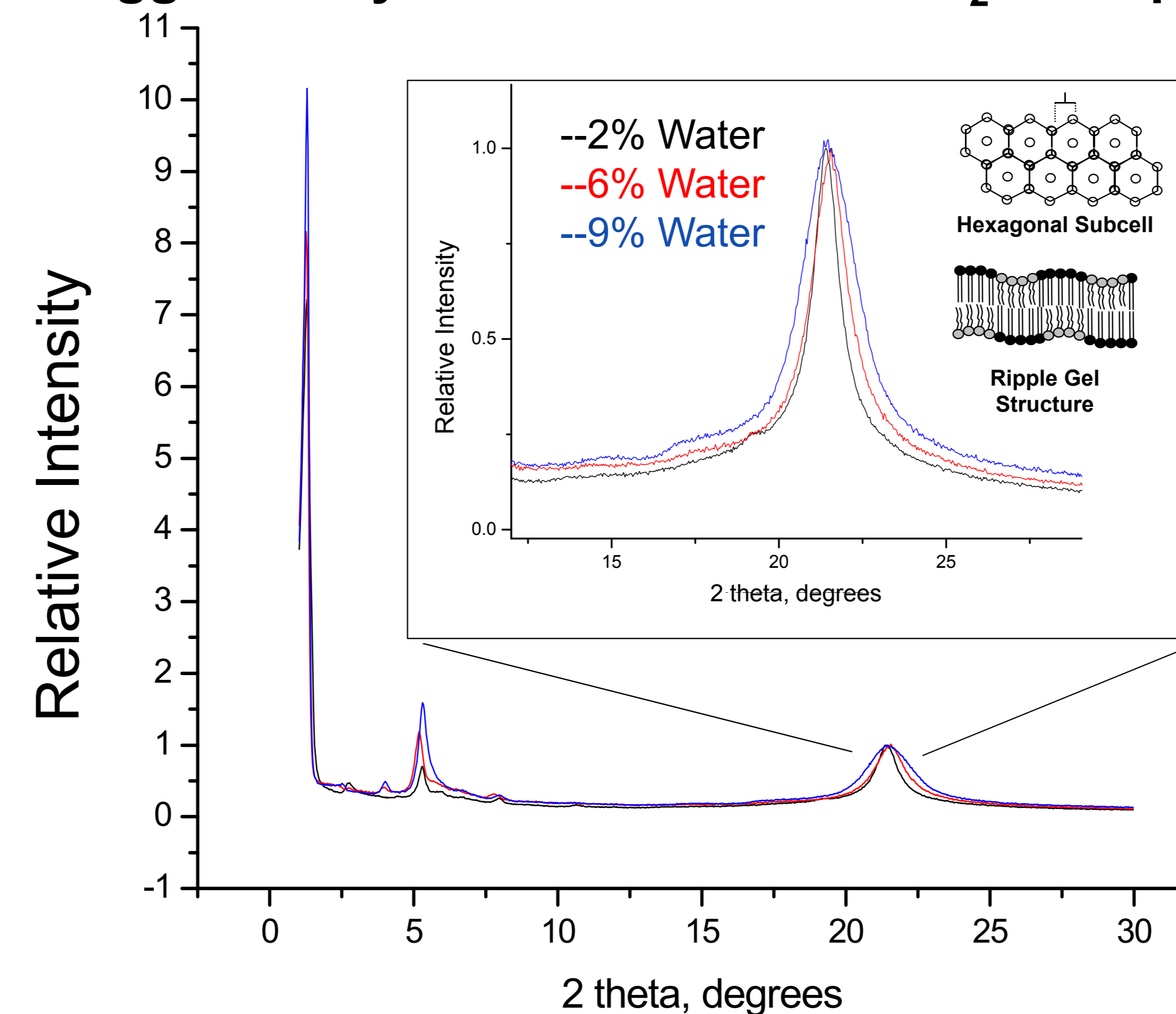
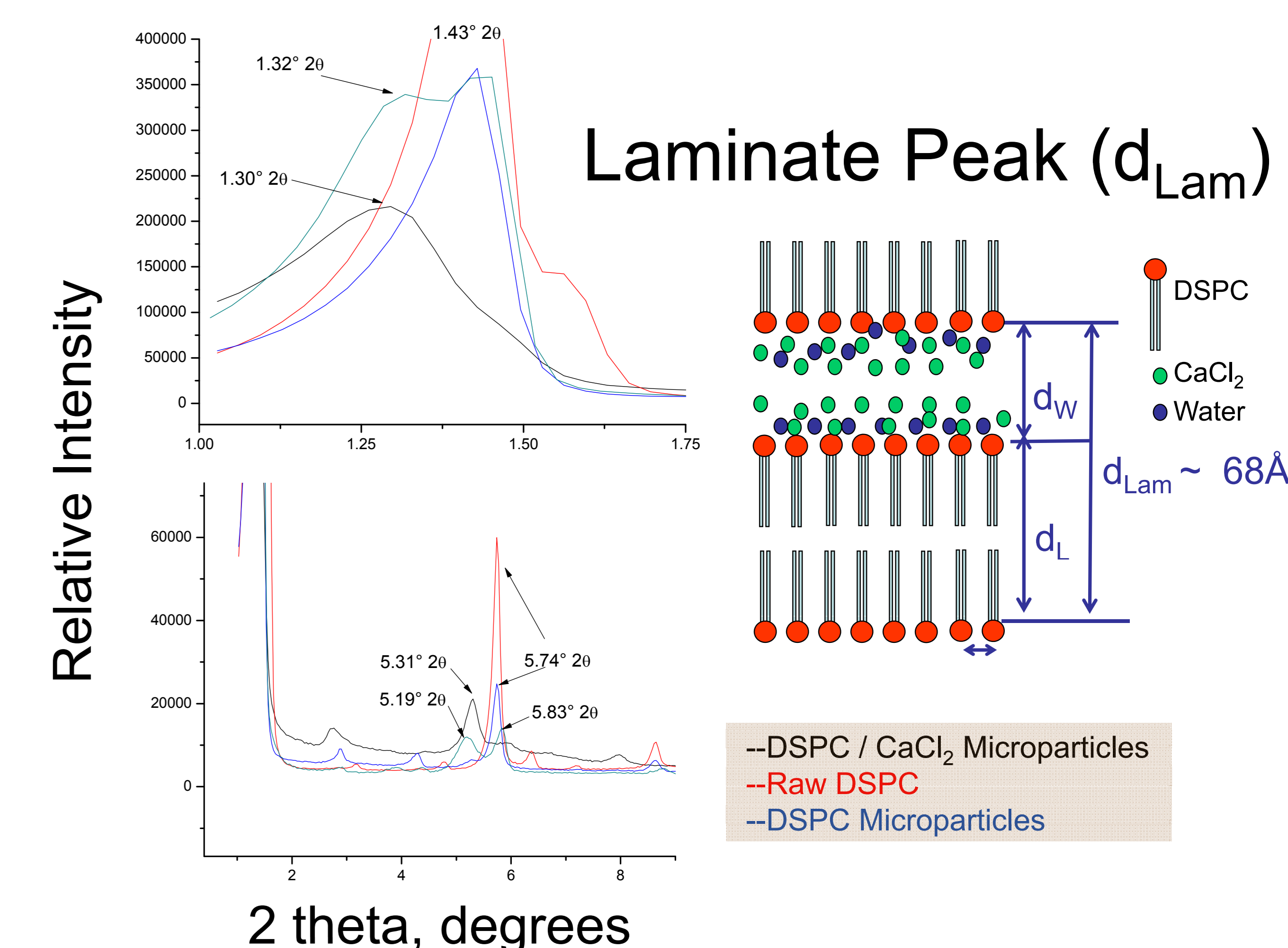


Fig 4: Presence of CaCl₂ imparts stability to lipid laminate by XRPD



Compared to a DSPC control, an increase in d-spacing in the presence of CaCl₂ is observed in the XRPD patterns. This indicates that CaCl₂ binds to the head groups of the lipid bilayer in the water/solvent (d_w) layer.

Conclusions

- DSPC phase behavior as a function of temperature and hydration resembles that of DPPC.
- The thermal stability of DSPC is enhanced by the presence of CaCl₂ as shown by the increase in the T_m
- The addition of CaCl₂ leads to a significant increase in the stability of the ripple gel phase ($P_{\beta'}$) at lower water content.
- The increase in T_m of the $L_c \rightarrow L_{\beta'}$ transition is greater than that of the $P_{\beta'} \rightarrow L_{\alpha}$ transition, indicating that CaCl₂ has a larger effect on the more ordered phases of DSPC.

References

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