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The influence of polaxamer surfactants on the thermal pre-transition of DMPC and DPPC liposomes

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Differential scanning calorimetry (DSC) has been employed extensively to investigate the gel to liquid-crystalline phase transition behaviour of synthetic and naturally occurring phospholipids. A small pre-transition peak is observed with some saturated phosphatidylcholines. The pre-transition is attributed to rotation of the polar head of the phospholipid molecules (Ladbrooke & Chapman, 1969) or to a co-operative shift of the rigid hydrocarbon chains before melting (Hinz & Sturtevant, 1972). However, it is claimed that the pre-transition of dimyristoyl-phosphatidylcholine (DMPC) and dipalmitoyl-phosphatidylcholine (DPPC) is due to structural changes in the lamellar lattice (Janiak et al, 1976).

Poloxamers are ABA block copolymers. They are nonionic, surface active materials with an amphipathic structure comprising of two hydrophilic polyoxyethylene (POE) moieties enveloping a hydrophobic polyoxypropylene (POP) moiety. Studies have shown that addition of Poloxamers to liposome formulations leads to an increase in blood circulation time (Woodle et al, 1992). However increased loss of an entrapped aqueous marker was also observed, suggesting that Poloxamers associate with the liposome bilayer but also may influence bilayer permeability. The use of gel-state lipids would potentially reduce bilayer permeability, although, Moghimi et al (1991) found no evidence of an interaction between liposomes and gel-state liposomes.

DMPC and DPPC films were hydrated with filtered deionised water. Poloxamers P338 and P407 were added to the aqueous phase of some formulations to give multilamellar vesicles (MLVs) with a final lipid concentration of 50 mg/mL. Following production, liposomes were incubated in a shaking water bath at 4, 18, 25 or 37°C, for 24 hours. High sensitivity DSC (Micro DSC 3, Seteram, France) was used to assess the interaction between components in the system. Each experiment was performed four times.

Incubation with Poloxamer P338 or P407 at 18, 25 or 37°C altered the thermal profile of DMPC MLVs. At low concentrations this was shown by a reduction in the pre-transition enthalpy. At higher Poloxamer concentrations the pre-transition was eradicated and the half height width of the main transition increased. However, the thermal profile of gel-state (DMPC or DPPC) liposomes was largely unaffected by incubation with Poloxamers. This indicates that P338 and P407 interact with phospholipid bilayers in the liquid-crystalline state but not with those in the gel-state, suggesting that the rigid bilayer structure inhibits the interaction. Exposure to five freeze-thaw cycles, as previously described (Castile & Taylor, 1996) caused a significant reduction in the pre-transition enthalpy of liposome / Poloxamer formulations (fig. 1). This suggests that freeze-thawing increased the interaction between the components of the system and therefore could be used to 'load' Poloxamers into the bilayers of gel-state liposomes.

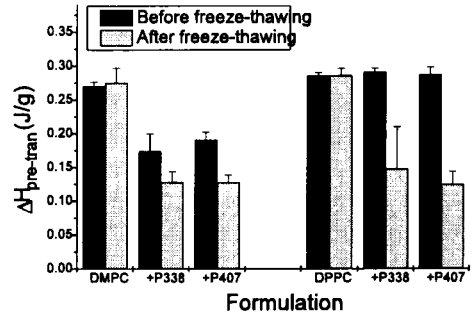

Figure 1. Pre-transition of 50 mg/ml DMPC and DPPC MLVs before and after five freeze-thaw cycles in the presence of 0.2%w/v P338 or P407

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