THE EFFECT OF CHLORPROMAZINE HYDROCHLORIDE ON THE THERMOTROPIC BEHAVIOUR OF DIMYRISTOYLPHOSPHATIDYLCHOLINE VESICLES

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Aqueous dispersions of phosphatidylcholines have been studied extensively as models for biological membranes. Many techniques exist to examine the thermotropic phase changes which occur in aqueous suspensions (liposomes). The thermotropic profile is modified when (a) solutes partition into the liposomal membranes or (b) the bilayer curvature changes as for example upon sonication. Thermotropic studies involving solute interactions with liposomes are of value in relating drug-membrane interactions to biological activity and for the characterization of drug-loaded liposomes as vehicles for drug delivery. This study examines chlorpromazine hydrochloride (CPZ) interaction with dimyristoylphosphatidylcholine (DMPC) vesicles in water and phosphate buffer, examined by densitometry, differential scanning calorimetry (DSC) and fluorescent probe analysis using anilinonaphthalene sulphonate (ANS) and diphenylhexatriene (DPH).

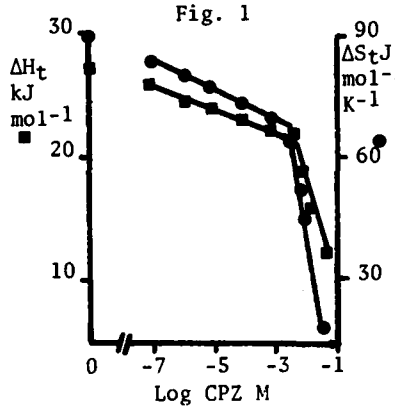
General agreement was found for the determination of the gel-liquid crystal transition temperature (T_c) using the three techniques. No differences were obtained using the two fluorescent probes which are located at different depths within the bilayer. ANS sited below the polar head groups gave more pronounced changes in fluorescent intensity compared with DPH which is located deep within the hydrocarbon interior. Although agreement in T_c occurred as a function of CPZ concentration over the range 1×10^{-8} to 1×10^{-6}M, T_c was not distinguishable using some techniques with higher CPZ concentrations. The presence of phosphate buffer (0.2M, pH 6.0) elevated T_c by up to 1.5°C compared with dispersions in water as indicated below.

CPZ (M)	DENSITOMETRY (WATER)	DENSITOMETRY (BUFFER)	DSC (BUFFER)	ANS (WATER)	DPH (WATER)
0	22.5	24.0	23.7	23.0	23.0
1×10^{-8}	22.1	23.75	-	22.5	22.5
1×10^{-7}	22.0	23.5	22.7	22.2	22.0
1×10^{-6}	21.9	23.0	22.1	22.0	22.0
1×10^{-5}	21.8	ND	21.5	22.0	22.0
1×10^{-4}	ND	ND	21.0	21.0	21.0
1×10^{-3}	ND	ND	20.5	20.0	ND

ND = Not distinguishable

More extensive DSC studies with 10% DMPC dispersions revealed the abolition of the pretransition endotherm at 16°C by CPZ concentrations $\geq 1 \times 10^{-4}$M. This pretransition arises from a change in the crystalline array whereby the mobility of the polar head groups change as does the orientation of the acyl chains. The main endotherm was observed to broaden as measured by the half-height width (HHW) at the same concentration and maximum broadening occurred at a concentration of 5×10^{-2}M. The peak was finally abolished at 1×10^{-1}M CPZ when the drug and lipid levels are almost equimolar. Peak areas were used to calculate enthalpy (ΔH_t) and entropy (ΔS_t) changes which reduced as the CPZ concentration increased (Fig. 1). Concentrations as low as 1×10^{-7}M CPZ can therefore be shown to possess a membrane destabilizing effect which was not evident by using the crude approach of HHW measurement.

Fig. 1



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