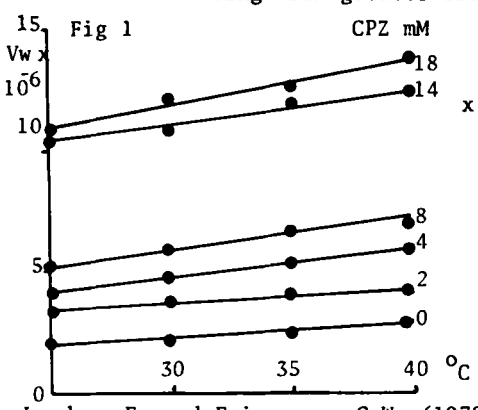
LIGHT SCATTERING STUDIES OF CHLORPROMAZINE INTERACTION WITH SMALL UNILAMELLAR DIMYRISTOYLPHOSPHATIDYLCHOLINE VESICLES

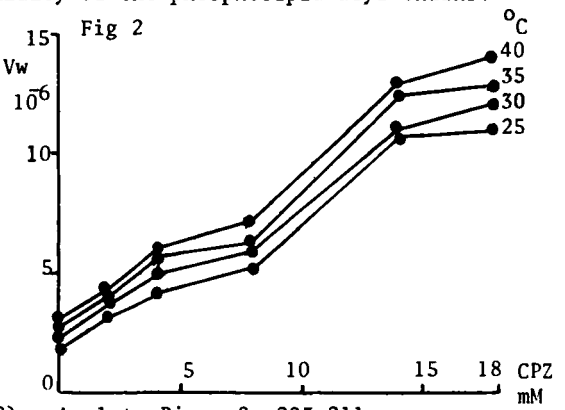
F.H. FARAH, J. HADGRAFT* and I.W. KELLAWAY, Welsh School of Pharmacy, U.W.I.S.T., Cardiff. *Department of Pharmacy, University of Nottingham, Nottingham.

The use of small unilamellar vesicles (SUV) as drug delivery systems confer the advantage of selectivity over multilamellar vesicles for drug delivery to a variety of sites including tumours and lymph nodes. Surface charge and fluidity are two other vesicle characteristics which influence the distribution of these particles within the body and hence directly influence target selectivity. Present studies investigate the effect of the model, cationic, surface active solute chlorpromazine hydrochloride (CPZ) on the size of SUV of dimyristoyl-phosphatidylcholine (DMPC) as a function of temperature and CPZ concentration.

SUV were prepared by sonicating a multilamellar dispersion of DMPC in 0.1M KCl for 30 min at 40°C and subjecting the resulting dispersion to gel fractionation on Sepharose 2B-CL. The elution profile (260nm) exhibited an excluded peak at the void volume due to large multilamellar vesicles and an included volume peak, the trailing edge of which was due to SUV. Bulked fractions from this part of the profile were therefore used as a source throughout this study of SUV as no difference in vesicle size could be detected for individual fractions using a SOFICA light scattering photometer. Phospholipid vesicle concentration was determined spectrofluorimetrically (London and Feigenson 1978). Stability of the dispersion was assessed over a period of 14 days when a slight increase in the scattered intensity at 90° (S_{90}) occurred suggesting a small degree of vesicle fusion. By determining S_{90} as a function of temperature, the phase transition temperature of DMPC was determined as 23°C. Weight average vesicle weight (Vw) was observed to increase linearly from 1.87×10^6 at 25°C to 3.08×10^6 at 40°C (Fig 1).

The CMC of CPZ was 12.8mM in 0.1M KCl at 25°C determined by surface tension measurement. Pre- and post-CMC of CPZ were equilibrated in the dark with the SUV dispersions for 72h at pH 6.2. Vw was determined over the temperature range of 25 to 40°C when a linear temperature dependence was observed for Vw for all concentrations of CPZ (Fig 1). For pre-CMC of CPZ, Vw increased with CPZ concentration (Fig 2). Little or no increase in Vw was found when CPZ levels were increased from 14 to 18mM. In the presence of SUV these concentrations of CPZ may not lead to micelle formation due to depletion of CPZ levels in the aqueous phase upon partitioning into the vesicles. The observed increased of Vw upon the partitioning of CPZ into the bilayer may reflect an increase in the volume of the aqueous interior of the vesicle together with an increase in bilayer thickness resulting from greater fluidity of the phospholipid acyl chains.





London, E. and Feigenson, G.W. (1978) Analyt. Bioc. 8, 203-211.

0022-3573/81/120068P-01$02.50/0