BINDING OF DOXORUBICIN TO NON-IONIC SURFACTANT VESICLES

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Non-ionic surfactant vesicles (NSVs) prepared from a hexadecyl triglyceryl ether (I) or dialkyl heptaglyceryl ether (II) have been studied as carriers of doxorubicin (DOX) (Cable et al., 1988a,b). They, and a third mixed surfactant (III) form stable vesicles with cholesterol or related lipids, the surface hydrophilic groups providing sufficient steric stabilisation to prevent association. The preparation of NSVs from a more hydrophobic analogue (IV) required the incorporation of charged moieties such as stearylamine (SA) or very hydrophilic entities such as the cholesteryl polyoxyethylene ethers. The evaluation of DOX-containing vesicles prepared from surfactant IV prepared with stearylamine surprisingly showed very low levels of free DOX in tissues, suggesting an interaction between drug and vesicular lipid.

Vesicles were prepared by sonication after hydration of surfactant IV: cholesterol:SA in the ratio 47.5:47.5:5 with DOX solution {5mg/mL}). The suspensions of vesicles which had a mean diameter, measured by PCS, of 194 nm were administered to AKR mice *via* the tail vein. Levels of DOX and metabolites were measured by HPLC (n=6 at each time point) in blood, liver, lung, spleen and heart. Some results are shown in Fig 1. While plasma levels of DOX are comparable to those measured after administration of systems without SA, low levels of DOX were obtained in other tissues. Dialysis experiments have shown that little drug is bound to the exterior of the vesicles in the first 6h after mixing, but release of drug from SA-containing vesicles is slow. DOX levels appear to be free, rather than total, levels of drug. The small effect of the system on the growth of subcutaneously implanted ROS tumours confirms these low levels and the slow release. The nature of the "complex" is not yet elucidated, but it is likely to be the result of a strong hydrophobic association because both the amine and drug possess the same charge. Histology shows that considerable numbers of vesicles are associated with the tumour vessels even 24h after administration, a finding confirmed by the plasma data; if vesicles were trapped in the liver and released drug slowly from that depot site, plasma levels would be expected to be lower than those obtained.

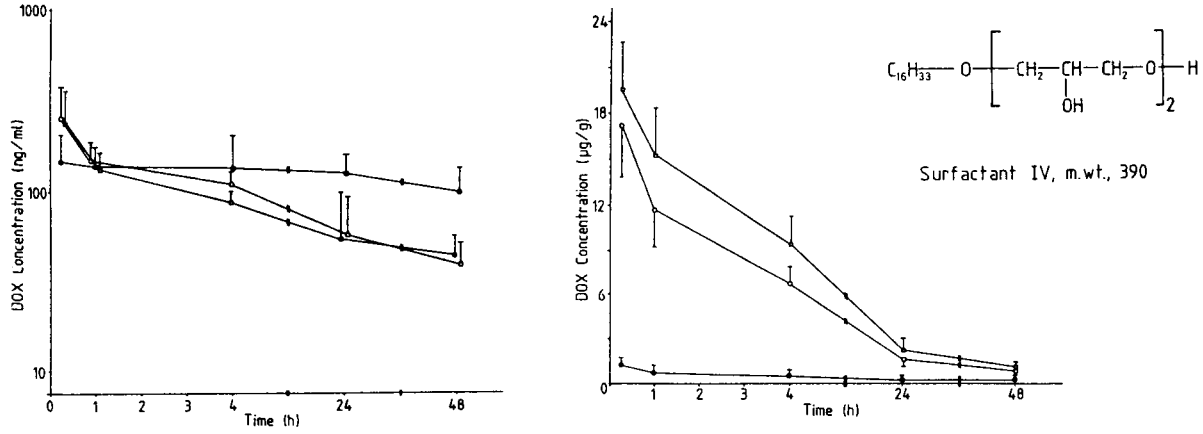

Fig. 1. Levels of DOX, in mice, after intravenous administration of the drug in (●) vesicles of IV:cholesterol:SA:47.5:47.5:5, (o) free DOX solution and (◘) solution plus NSVs mixed prior to injection (dose 5mg/kg). *Left*: plasma and *Right*: in heart tissue.

Cable, C., Florence, A.T. (1988) J.Pharm.Pharmacol. 37: Suppl. 30P
Cable, C. et al (1988) Ibid, 37: Suppl. 31P