INTERACTIONS OF SURFACTANTS AND LOW DENSITY LIPOPROTEIN (LDL)

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LDL (density 1.019-1.063g ml^{-1} exists as spherical particles (diameter 22nm) consisting of a lipid core of triglycerides and cholesteryl esters surrounded by a monolayer of cholesterol, phospholipids and an uncharacterized protein-apoprotein B (Kirchhausen et al 1980). Unlike exogenous colloidal particles, LDL is not accumulated in the liver but binds to specific receptors on peripheral cells before being internalized as a source of cholesterol. Gal et al (1981) have shown that LDL accumulates selectively in tumour cells. These features suggest that LDL might be a useful delivery system for lipophilic chemotherapeutic agents. Numerous attempts to replace the cholesteryl esters with labelled molecules have met with limited success (Craig et al 1982) yet in vivo ester exchange occurs readily, being catalysed by a cholesteryl ester exchange protein.

Assuming this enzyme affects particle integrity to allow ester exchange, the aim of this work was to investigate the effects of various surfactants on LDL as a prelude to the loading of LDL particles with lipophilic drugs. LDL was extracted from normal plasma by zonal centrifugation. Solutions were concentrated to approximately 5 mg LDL/ml in isotonic phosphate buffer (pH 7.4), sterilized by filtration (0.22um) and stored in ampoules under N_2, at 4°C. Increasing volumes of various surfactants in buffer were added and the changes in the equivalent hydrodynamic radius and polydispersity followed by quasi-elastic light scattering (Fig. 1.).

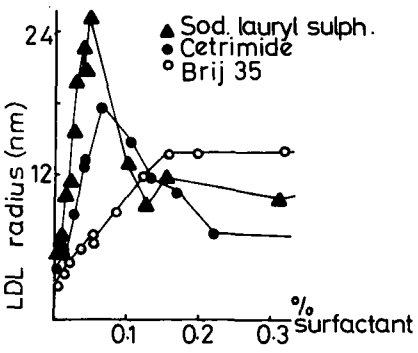

Fig. 1. Radius of LDL particles in presence of surfactants.

Control experiments showed that the changes in radius were not due to aggregation caused by the mixing process or time dependent changes in LDL. Furthermore, there was no significant change in polydispersity, suggesting a uniform growth of all particles rather than the formation of a few large aggregates. The increases are greater than would be expected for monolayer adsorption, and multilayer adsorption is ruled out since the molar ratio (e.g. cetrimide to LDL) at the maximum radius is only 900:1. Assuming total adsorption of cetrimide a ratio of 3000:1 is required for monolayer coverage. Possible explanations are: intercalation of surfactant leading to gross dimensional changes (as occurs in mixed micelles) or partial detachment of the apoprotein. The decreases in radius at higher concentration of cetrimide and sodium lauryl sulphate might be due to complete disruption of the LDL particles. If this is the case the use of a nonionic to achieve drug loading would seem preferable.

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