THE EFFECT OF LIPOSOMAL CHARGE ON DRUG TOXICITY AND EFFLUX

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Considerable interest has been shown recently in colloidal drug delivery systems with an aim to achieving target therapy. The concept of liposomes as drug carriers is now regarded as a feasible proposition worthy of continued investigation. The surface charge of liposomes may be modified by incorporating ionic lipids into the phospholipid bilayers, and/or the entrapment of charged drug molecules. It has been demonstrated that the surface charge may modify the distribution of liposomes within the body, (Jonah & others 1975; Juliano & Stamp, 1975) and to influence the permeability of liposomes to ions in that positively charged liposomes are impermeable to cations whilst a negative charge results in preferential anion permeability. (Papahadjopoulos & Watkins 1967).

It has been previously shown (Chawla, R.S. & others 1978) that the uptake and release rate of the dibasic drug chloroquine from liposomes was pH dependent. In this study the zeta potential of the liposomes has been varied by the incorporation of ionic lipids and the influence of surface charge on drug uptake, efflux and toxicity determined. Electrophoretic mobilities (E.M.) were determined at 25^{o} in a capillary cell of a Rank Mk II Microelectrophoresis apparatus.

The E.M. of liposomes was dependent on the ionic strength of the supporting electrolyte which was therefore kept constant throughout the experiments. Dicetylphosphate and stearylamine were used to obtain negative and positive liposomes respectively. Similar mobility patterns were observed with egg or synthetic saturated phosphatidylcholines. Addition of cholesterol to modulate bilayer fluidity had no effect on the E.M. For pH < pka_1 of chloroquine a positive charge was induced in 'neutral' liposomes by ionisation of the chloroquine molecule, with the E.M. being reduced around pH 8 to 10. Addition of chloroquine to positively charged liposomes increased the E.M. whilst reducing the mobility of negatively charged liposomes.

Because of the observed variation in zeta potential, preliminary studies were carried out to observe the response of cultured mouse peritoneal macrophages to liposome preparations added in vitro as an indicator of toxicity. Positively charged liposomes were found to be toxic whilst neutral and negatively charged liposomes were well tolerated by the cells. These observations indicate that negatively charged or neutral liposomes should be used in further investigations of liposome - cell interactions.

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