THE FORMULATION OF CORTISONE ESTERS IN LIPOSOMES

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Multilamellar liposomes (MLV) have been suggested as carriers of both hydrophilic and lipophilic drugs and have been shown to successfully entrap both species (Gregoriadis 1973). Studies involving the use of liposome formulations of corticosteroid esters have shown their potential as sustained release devices (Shaw, Knight and Dingle 1976). In this work we have investigated the kinetics of liposomal retention of a homologous series of Tritium labelled cortisone-21-esters.

All cortisone esters were used in tracer quantities. Films of steroid and lecithin were prepared by rotary evaporation from ethanolic solution. All traces of solvent were removed from the films in vacuo. MLV were formed by mechanical shaking after the addition of normal saline. The suspension was maintained at 37°C for 120 h to allow equilibration of the cortisone ester between bilayers and saline. The liposomal suspension was diluted 10 fold and release rates followed by scintillation counting of the supernatant after centrifugation for 50,000 gh. The release data of the different esters was normalised to facilitate comparison of the profiles of esters starting at different states of partitioning. First order rate constants (k) were calculated from plots of log normalised percentage retained versus time.

For dipalmitoylphosphatidylcholine (DPPC) MLV a plot of log k versus cortisone-21-ester chain length in carbon atoms (n) shows as linear portion between n = 6 and n = 14. This relationship is described by the equation

$$\log k = 5.19 \times 10^{-2} n - 1.21$$

Cortisone acetate and butyrate deviate from this relationship as the ester length is insufficient in comparison with the bulk of the steroid nucleus to allow orientation for alkyl chain interaction of the bilayer and ester. Efflux of cortisone was too fast to be followed by this method. A second linear relationship was seen between n = 16 and n = 22, as described by the equation

$$\log k = -1.59 \times 10^{-3} n - 1.94$$

Hence the release kinetics of cortisone palmitate, stearate and behenate are very similar. This is probably due to total penetration of the liposomal bilayer being hindered, by the chain length of the ester exceeding that of DPPC. Evidence from differential scanning calorimetry supports the theory that retardation of release is due to increased interaction of the steroid ester with the alkyl chains of the bilayer. Partitioning and efflux from distearoylphosphatidylcholine and egg lecithin liposomes was erratic. Efflux from liposomes of dimyristoylphosphatidylcholine was reproducible, but approximately twice the rate from DPPC liposomes.

Gregoriadis, G. (1973) F.E.B.S. Letters 36, 292-295
Shaw, I.H. et al (1976) Biochem. J. 158, 473-476