34P

THE UPTAKE OF LIPOSOME-ENCAPSULATED CARBOXYFLUORESCEIN FROM THE RAT LUNG

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The efficient transfer of many pulmonary administered drugs into the blood indicates the potential of the lung route for the therapy of systemic conditions. One advantage of the pulmonary route is that it can be utilized by sustained-release formulations such as phospholipid vesicles. This work characterises the pulmonary absorption of a marker compound, 6-carboxyfluorescein (CF), when entrapped in neutral and negatively-charged liposomes.

Multilamellar liposomes composed of either dimyristoylphosphatidylcholine (DMPC)/cholesterol (1:1 mol ratio, neutral), or DMPC/cholesterol/dicetylphosphate (1:1:0.2, negatively-charged), containing 0.25M CF, were prepared by the hydration of lipid films. These were reduced in size by probe sonication and the unentrapped dye removed by a combination of ultrafiltration and gel-filtration. Liposome preparations (113-139nm) or free dye were administered as a fluid instillation (0.1ml) to the trachea of pentobarbitone-anaesthetised male wistar rats (200-250g). Blood samples were removed from a cannulated carotid artery and the concentrations of free and liposome-entrapped dye determined in the diluted plasma by fluorimetry in the absence and presence of Triton X-100 respectively. Previous studies had indicated that the intravenous disposition of CF was dose-independent at doses of 0.5-2mg/kg (Woolfrey et al 1985).

Table 1: Absorption Parameters for Liposome-Encapsulated CF (Neutral and Negatively-Charged Vesicles) After Administration to Rats at 2mg/kg

	Liposome Type		Stat. Diff.
	Neutral (n=5)	Negatively-charged (n=6)	(t-test)
F (%)	39 (47-33)	50 (58-43)	$p<0.02$
MRT (min)	736 (1095-495)	296 (447-196)	$p<0.005$

Upper and lower 95% confidence limits are shown in parenthesis.

The pulmonary absorption of free CF (0.5 & 2mg/kg) occurred with a mean (95% confidence limits) residence time at the absorption site (MRT) of 137 (104-179)min and fraction available (F) of 108 (86-141)% respectively. Liposome-encapsulation of CF significantly reduced F and increased MRT compared to the absorption of the free marker (Table 1). Analysis of blood samples in the presence and absence of Triton X-100 indicated that CF containing liposomes were not transferred into the blood. CF entrapped in the neutral liposomes had a significantly longer MRT and lower F compared to CF encapsulated in the negatively-charged species (Table 1). The loss of entrapped dye (latency, mean ±S.E.M.) from the neutral and negatively-charged vesicles when suspended in phosphate buffered saline at 37°C was 0.23±0.06 and 0.61±0.07 %latency/h respectively. Although significantly different ($p<0.01$), this difference in latency loss could not account for the variation in bioavailability between the two liposome species.

Woolfrey, S.G. et al (1985) Int. J. Pharm. 26: 35-43.