IN-VITRO EVALUATION OF SPONTANEOUS LIPOSOME FORMATION FOLLOWING AEROSOLISED ADMINISTRATION OF PHOSPHOLIPID

S.J. Farr, I.W. Kellaway and B. Carman-Meakin*, Welsh School of Pharmacy, UWIST, Cardiff CF1 3XF and *Riker Laboratories, Loughborough LE11 1EP.

A previous communication (Farr et al, 1985) has cited the potential of liposomal delivery systems in sustaining the duration of action of inhaled bronchodilator drugs. In theory, administration could be performed by nebulisation of an aqueous dispersion of drug loaded, preformed liposomes but may prove of limited application due to the poor stability of phospholipid vesicles on storage. Alternatively, the incorporation of phospholipids within the inert environment of a chlorofluorohydrocarbon (CFC) based pressurised pack should circumvent such problems and, in addition, allow the spontaneous formation of liposomes in situ following entry of the emitted aerosol dose into the humid environment of the lung.

Solution phase pressurised packs (10 ml volume; 50 µl metered dose) were formulated to contain 0.5 to 5 %^{W}/v purified egg phosphatidylcholine (PC) in two CFC blends: Blend 1, 23/77/0 (vapour pressure, 21^{o}C = 480 kPa), blend 2, 30/41/29 (vapour pressure, 21^{o}C = 343 kPa) of Arcton (ICI, Ltd) 11,12 and 114 respectively. In order to evaluate the potential of spontaneous liposome formation, up to 20 actuations were fired from primed, inverted units into an airstream (50 1min^{-1}) generated downstream of a single stage liquid impinger (SLI) positioned within a laminar flow cabinet. Aliquots of the receptor fluid (particle free, distilled water) were removed and the presence of liposomes determined by observation under TEM and by photon correlation spectroscopy. Further aerosol characterisation was conducted on similar pressurised units spiked with 1.2 µCi ^{14}C dipalmitoyl PC using a multistage liquid impinger (MLI; Bell et al, 1973) and scintillation counting for activity deposited on each stage.

Aerosol droplets collected within the SLI displayed time dependent size changes as a result of slow propellant evaporation before equilibration at approx. 30 min. TEM on equilibrated samples confirmed the presence of discrete populations of multilamellar liposomes. The mean size of liposomes so formed were statistically equivalent for pressurised packs composed of 0.5 to 2 %^{W}/v egg PC in blends 1 or 2 and ranged from 334±44 to 355±25 nm. Liposomes formed from the formulation containing 5 %^{W}/v at 480 kPa were statistically larger ($p < 0.05$) with a mean size of 591± 41 nm. Aerosol droplets entering the MLI are considered equivalent to the effective dose delivered to the respiratory tract, particularly those capable of penetration into the latter stages (3 and 4). Such droplets exhibit aerodynamic diameters < 5.5 µm and , generally, are accepted as the most useful in therapeutic terms (ie. the respirable fraction, RF). Egg PC concentration was critical to the amount of aerosolised dose within the respirable range (table). Increasing phospholipid concentration reduced RF as a result of a combination of greater impaction within the oral adaptor and throat and an increase in MMAD of aerosol entering the MLI. Similar effects occured on reduction of vapour pressure of the propellant blend. Formulation variables, therefore, will exert a significant influence on the phospholipid dose deposited within the lung. From the evidence of this study and in view of the humid environment of the lung, the deposited phospholipid should be capable of spontaneous liposome formation in situ thereby providing a sustained release reservoir for suitable drugs included within the formulation.

EGG PC (%^{W}/v) IN BLEND 1	RF (%) ± SD, n=3
0.5	23.87 ± 6.09
1.0	20.02 ± 5.68
2.0	16.32 ± 1.84
5.0	4.90 ± 2.58

Bell J.H. et al (1973) J. Pharm. Pharmacol. 25: 32P
Farr, S.J. et al (1985) J. Pharm. Pharmacol. 37: 61P