COMPARISON OF PARTITIONING AND EFFLUX IN LIPOSOMES PREPARED USING AEROSOLISED PHOSPHOLIPID AND A CONVENTIONAL METHOD

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Previous studies (Farr, 1984) have demonstrated the phenomenon of spontaneous liposome formation following deposition of aerosolised phospholipid particles, generated from a solution type pressurised pack, within an aqueous environment. As part of a programme to evaluate the potential of such systems to impart sustained or controlled release to pulmonary delivered drugs, this further study aimed to assess in vitro the partitioning and release of a model compound in liposomes so formed, and also to undertake comparison with conventionally prepared vesicles (ie. by hydration of a thin lipid film). Hydrocortisone octanoate, which partitions favourably into liposomes (Arrowsmith et al, 1983), was selected as the model compound to assist in the accurate detection of entrapment and efflux in suspensions composed of very low phospholipid concentration such as are formed by the aerosolised method.

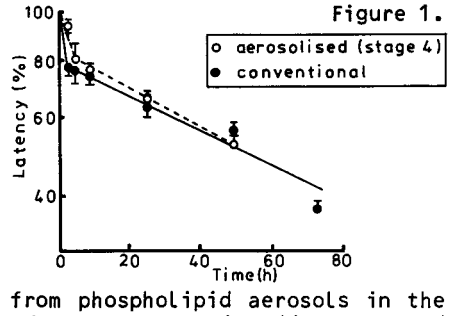
Pressurised packs (10 ml) were formulated to contain 1 %^{w}/v egg phosphatidylcholine (PC) (spiked with 1.59 μCi ^{14}C dipalmitoyl PC) and 25 μg of hydrocortisone octanoate (spiked with 4.15 μCi of tritiated ester) in a chlorofluorhydrocarbon blend (Arcton, ICI Ltd, 11:12, 23:77). Each unit was sealed with a 50 μl metering valve (Neotechnic) and exhibited an internal pressure of 536 kPa at 25°C. Aerosol characterisation was conducted by firing 40 actuations from primed, inverted units into a multistage liquid impinger (MLI) followed by dual scintillation counting for activity at each stage. Partitioning of the steroid ester in liposomes formed within the receptor fluid (0.9 %^{w}/v saline) of stages 3 and 4 was determined on equilibrated (37°C) samples after separation of the free and membrane associated fractions by ultracentrifugation. Partitioning data for conventional liposome systems were determined on suspensions formed by hydrating mixed films of egg PC (25 mg) and steroid ester (0.1mg spiked with 0.83 μCi of the tritiated compound) with 50 ml of normal saline. Efflux from both systems was followed by monitoring appearance of steroid ester in the bulk phase after a 10 fold dilution.

The results in table 1 demonstrate that partitioning of hydrocortisone octanoate in egg PC liposomes prepared by the conventional or aerosol method is similar, and is independent of the stage on which the liposomes were generated (ie. originating from different size aerosol fractions). Similarly, figure 1 shows equivalent release kinetics for the diluted systems.

Table 1.

SYSTEM	PARTITION COEFF. AT 37°C EGG PC / SALINE (x 10^{3}; ± SD)
CONVENTIONAL	5.50 ± 1.04, n=4
AEROSOLISED:	
STAGE 3	4.50 ± 1.66, n=3
STAGE 4	5.68 ± 0.95, n=3

Figure 1.



The results suggest that liposomes produced from phospholipid aerosols in the MLI possess similar structural characteristics to conventionally prepared liposomes. This should allow prospective drug candidates intended for incorporation into aerosol generated liposomes to be initially screened using more conventional methods of liposome production.

Arrowsmith, M. et al (1983) Int. J. Pharm. 14: 191.
Farr, S.J. (1984) PhD Thesis, University of Wales.