J. Pharm. Pharmacol. 1998, 50 (Supplement): 158

The delivery of liposomes from jet nebulizers

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The stability of liposomes during jet nebulisation depends on the liposome size and bilayer composition (Taylor et al, 1990). The present study investigated the relationships between liposome size, composition and the size of aerosol droplets produced by four jet nebulisers, with respect to disruption of vesicular structures, retention of liposomes, and entrapped drug release.

Multilamellar liposomes (MLVs) produced from egg phosphatidylcholine (eggPC), eggPC with equimolar cholesterol (chol) and dipalmitoylphosphatidylcholine (DPPC) with equimolar chol, were extruded through polycarbonate membrane filters, to a mean size of 0.6, 1, 2.5 and 5 μm. Aerosols were generated from liposomes (10 mg/mL) using Cirrus (DHD Intersurgical, UK), Pari-LC (Pari-Werk, Germany), Respirgard II (Marquest, USA) and Sidestream (Medic Aid, UK) nebulisers, driven by compressed nitrogen. Liposomes and aerosols were sized by laser diffraction (Malvern 2600C, Malvern, UK). Liposomes were sized in the nebuliser chamber, prior to and during nebulisation, and the release of an entrapped aqueous soluble drug, sodium cromoglycate, was determined by UV analysis. Changes in lipid concentration within the nebulisers, was assessed by drying and subsequent weight measurements.

For each nebuliser studied there was a time-dependent reduction in mean liposome size, indicating disruption of vesicular structures. This was most marked for eggPC liposomes, and larger liposomes (2.5 and 5 μm) of all compositions. Cholesterol containing liposomes underwent less marked size reductions, and released smaller amounts of entrapped drug. However, although the Respirgard II nebuliser produced the smallest aerosol size, and caused greatest reduction in liposome size, there was not a direct correlation between aerosol size and vesicle disruption (fig 1). The Cirrus, although producing relatively large aerosol droplets, caused relatively great vesicle disruption. This reflects specific features of the design of the individual nebuliser, such as the dimensions and/or geometry of the jet or the baffles of the nebuliser, the way in which gas and fluid are mixed in the nebuliser nozzle, and frequency of fluid recycling. The presence of open vents (Sidestream), which reduce droplet size by evaporation, may also be influential.

The lipid concentration in the nebuliser reservoir increased during nebulisation. This increase was greatest for larger liposomes, and for the Sidestream and Respirgard nebulisers, which produced the smallest aerosols. For 0.6 and 1 μm liposomes the increase in lipid concentration was comparable to increases measured for sodium chloride solutions. Thus, small liposomes behaved like conventional solutes, with the increase in concentration being principally due to evaporation of bulk water in response to the dry gas jet (Ferron et al 1976). However, for 2.5 and 5 μm liposomes, a size-selective process operated, which varied between the different nebulisers. In particular, the design of the Sidestream nebuliser encouraged the retention of liposomes, whilst the Cirrus and Pari-LC had smaller effects.

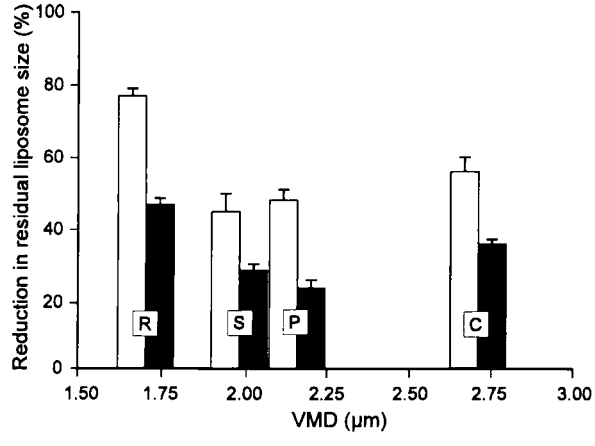

Fig 1. Relationship between mean aerosol size produced by C=Cirrus, P=Pari, R= Respirgard, S=Sidestream nebulisers and reduction in mean size of residual eggPC (□) and DPPC/chol (■) liposomes , original mean size 5 μm (n=3 ± sd)

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