THE HYDROLYSIS AND INCORPORATION OF CROMOGLYCATE ESTERS INTO LIPOSOMES

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Studies of liposomally entrapped drugs for pulmonary administration have included the evaluation of encapsulation efficiency of hydrophilic compounds such as sodium cromoglycate (Taylor et al 1990). The maximum amount entrapped is governed by the aqueous solubility of the drug. Generally water soluble drugs are poorly incorporated compared to more hydrophobic i.e. bilayer associated drugs. This study examines the feasibility of using lipophilic esters of sodium cromoglycate to increase drug loading and to sustain the delivery of cromoglycate.

Two diesters of cromoglycate were studied (dipentyl and dipivalyl) to determine the influence of ester hydrophobicity on encapsulation efficiency and the rate of free cromoglycate formation following diester hydrolysis. The latter was monitored by reverse phase HPLC on a Spherisorb ODS 5µm column and monitored at 326nm. 800µl of a 5 x 10^{-4} g ml^{-1} diester solution in acetonitrile was incubated with 10ml of 50:50 MeCN:phosphate buffered saline, a solvent system selected to ensure ester solubility. DSC was used to determine the level of diester incorporation in DPPC liposomes (10% w/v) by examination of the principal endotherm as a function of diester concentration. Fig.1 shows the hydrolysis of the dipivalyl ester according to the equation diester $\xrightarrow{k1}$ monoester $\xrightarrow{k2}$ cromoglycate. The hydrolysis rates observed were approximately 39 times faster for the dipivalyl compared to the dipentyl ester (Table 1). Analysis of the DSC data indicated that a maximum of 2.5 - 5 mole % of the dipivalyl ester incorporation into the DPPC liposomes occurred before the drug precipitated as a separate microcrystalline phase. TEM negative-staining preparations were used to confirm the DSC results. Concentrations of the dipivalyl ester in excess of 2.5 mole % resulted in the formation of two distinct phases, one vesicular the other microcrystalline. The use of a lipophilic prodrug in this instance failed to achieve a high encapsulation efficiency.

This study has shown that the cromoglycate esters alone were slowly hydrolysed in aqueous media and may therefore be of value as a slow release pulmonary formulation by virtue of their poor aqueous solubility. Liposomal encapsulation would offer no formulation advantage. However, it is conceivable that the lipophilic esters would be absorbed from the lung before hydrolysis was complete thus negating the advantage of using more lipophilic species.

Fig. 1 **Time course of the different species in the hydrolysis of the dipivalyl ester**

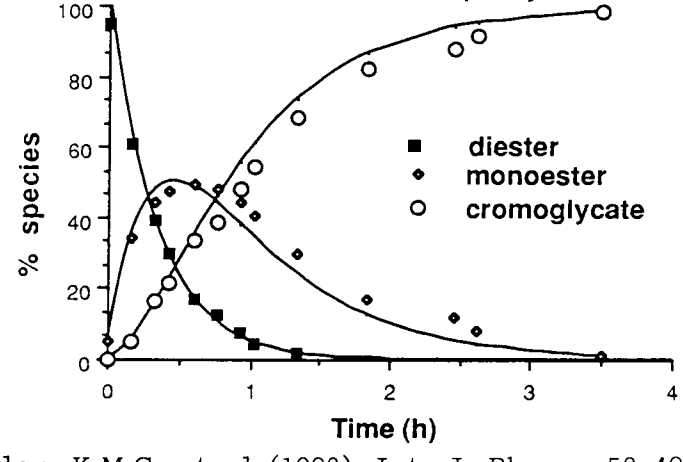

Table 1.

Diester	k_1 (h^{-1})	k_2 (h^{-1})
Pivalate	2.99	1.425
Pentyl	0.08	0.04

Taylor, K.M.G. et al (1990), Int. J. Pharm. 58 49-55