PERCUTANEOUS ABSORPTION OF METHYL SALICYLATE FROM POLYETHYLENE GLYCOL VEHICLES

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It has been reported that vehicles containing polyethylene glycols (PEG) could affect the absorption of salicylates through the skin (Cotty et al 1960). Suggested reasons are an increase in vehicle viscosity and/or a reduction in thermodynamic activity due to drug-vehicle interaction. We have therefore investigated the in vitro and in vivo release characteristics of such systems and the effect of the molecular weight of the PEG using methyl salicylate and salicylic acid.

In vitro drug release was followed using a standard diffusion cell with a silastic membrane (Billups and Patel 1970). A linear relation between release and square root time was observed and the higher the molecular weight of the PEG the lower the release rate. Apparent diffusion coefficients (D_A) were obtained from the gradients of the plots (Table). Viscosity effects were separated from drug-vehicle interactions by measuring the thermodynamic activity of the drug in the base, in the form of a vehicle-vapour phase-partition coefficient. The technique of head space analysis was employed, using closed containers with PTFE lined caps. Vehicle-drug samples were stored for 40 days before GLC analysis. Relative diffusion coefficients (D_R) at constant thermodynamic activity were derived using PEG 200 as an arbitrary standard state. The fall in D_R with PEG molecular weight is attributed to the viscosity effect. In vivo absorption was followed using a rabbit ear model. The semi-solid vehicle was applied to one ear of a lop rabbit and blood samples were collected from the contralateral side. Plasma salicylate concentrations were determined by HPLC. An increase in the salicylate concentration in the base gave a corresponding linear increase in derived pharmacokinetic parameters (peak concent. area under curve). At a given concentration of drug the amount of salicylate absorbed (as expressed as the area under the plasma level time curve (A_p)) decreased with increase in molecule weight of the PEG (Table). An excellent in vitro-in vivo correlation exists between D_R and A_p. The absorption of methyl salicylate was greater than that for salicylic acid for all grades of PEG. This is due to the difference in drug-base interactions between the two molecules as well as the higher partition coefficient of the ester over that of the free acid.

Table In vitro and in vivo parameters for the release of methyl salicylate (10%) from PEG (30°).

PEG	D_A $cm^2 s^{-1}$ $\times 10^{-7}$	Head Space Concentration $\mu g\ ml^{-1} \times 10^{-2}$	D_R $cm^2 s^{-1}$ $\times 10^{-7}$	Area under plasma curve (n = 3)
200	-	5.97	-	-
600	1.86	4.11	3.79	1105 ± 80
850	1.05	3.33	3.37	990 ± 120
1500	0.48	2.67	2.40	760 ± 90
2000	0.20	2.01	1.76	520 ± 100

Billups, N.F. and Patel, N.K. (1970) Amer. J. Pharm. Ed. 34, 190
Cotty, V.F. et al (1960) J. Soc. Cosmet. Chem. 11, 97

0022-3573/81/120097P-01$02.50/0