

THE PARTITIONING OF HYDROCORTISONE AND ITS ESTERS INTO STRATUM CORNEUM IN-VITRO—IN-VIVO CORRELATIONS

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The principal barrier function of the skin resides almost entirely in the horny layer or stratum corneum which consists of alternating lipophilic (skin fat and dry keratin) and hydrophilic (contents of corneocytes) layers (Jacobi, 1969). This work examines the first stage of percutaneous absorption, namely the partition controlled passage of drugs into the outermost cell layer of the stratum corneum.

In vitro partition coefficients ( $K_m$ ) between human stratum corneum and 0.9% saline were determined for  $^{14}\text{C}$  hydrocortisone ( $C_0$ ) and its C21 alkyl esters - acetate ( $C_2$ ), propionate ( $C_3$ ), valerate ( $C_5$ ), hexanoate ( $C_6$ ) and octanoate ( $C_8$ ).  $K_m$  was calculated from residual activity in the solvent after 48 hr incubation. Free energies of partitioning were negative and decreased rectilinearly with increasing carbon number. Free energies were calculated from  $\Delta G = -RT \ln K$  & entropies from  $T\Delta S = \Delta H - \Delta G$ . The relative values of the three parameters indicated that for the longer chain esters, the process was entropy controlled.

In vivo studies at ambient temperature were undertaken of steroids applied in acetone to a  $1 \text{ cm}^2$  dorsal area of shaved mouse skin. Activity was monitored periodically by surface Geiger counting and plots constructed of the temporal change in log % of the initial activity at the application site (Fig. 1) SEM  $\leq 0.04$ . After initial decay periods of 50–65 min, depending on the steroid, the activity remained constant. This plateau value was taken as a measure of the drug remaining at the skin site after partitioning into the outermost cell layer had occurred, a fast process compared with diffusion through the stratum corneum.

Fig 1.

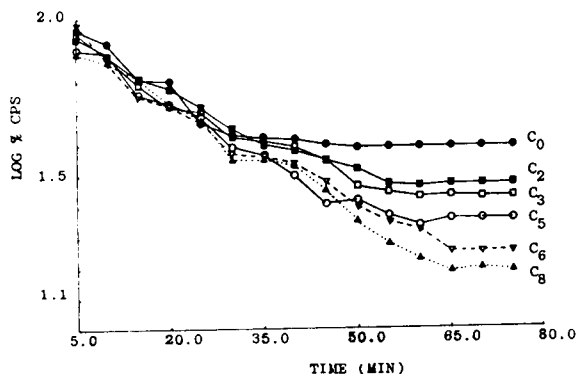
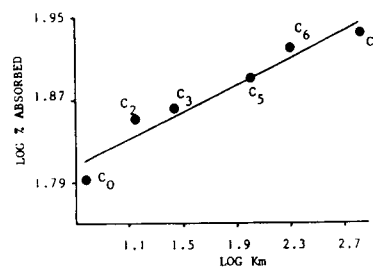


Fig 2.



The log % absorbed from the skin surface was plotted versus log  $K_m$  (Fig. 2) to give the linear relationship:

$$\text{Log \% absorbed} = 0.064 \log K_m + 1.76 \quad (n=6; r=0.963);$$

thus confirming the value of in vitro partitioning data to the resolution of the initial stages of the percutaneous transport process.

Jacobi, O. Die Inhaltsstoffe des normalen Stratum corneum and Callus der menschlichen Haut. Arch. Klin. Exp. Dermatol. 233, 383–406 (1969).