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A NOVEL IN-VITRO MODEL FOR ASSESSMENT OF BUCCAL ABSORPTION OF PEPTIDE DRUGS AND THE INFLUENCE OF PENETRATION ENHANCERS

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In recent years increasing interest has been shown in the therapeutic potential of peptides and hormones and their analogues, but oral administration continues to be an ongoing problem. Some promise has been shown in nasal administration of insulin and calcitonin and the buccal route may offer similar potential as absorbed drugs are subject to neither acid degradation nor first-pass metabolism. With respect to diffusion of water, and a series of structurally unrelated drugs, it has been shown that dekeratinised skin (ie dermis which has been exposed by stripping away the stratum corneum) provides excellent correlation with freshly excised buccal mucosa (Galey et al 1976). Consequently an in vitro model, comprising dekeratinised, hairless- mouse skin was utilised to determine the potential buccal absorption of a very water soluble, tripeptide TRH analogue - RX77368 (fig 1), and the effects of penetration enhancers assessed. The buccal model was based on a glass diffusion cell. Both mucosal and serosal solutions contained pH6.9 buffer (the approximate pH of the oral cavity), were maintained at 37°C and stirred throughout. Tritiated RX77368 was added to the mucosal solution and regular samples of serosal solution withdrawn for analysis.

At this pH RX77368 was >99% dissociated, thus diffusion was neither rapid nor extensive (6.0 ± 1.4% in 4 hours) and this may be explained by the low partition coefficient (log P (octanol:water) << 0.01) and high water solubility ($>100 mgml^{-1}$) at pH6.9. When 0.075% (w/v) sodium lauryl sulphate (SLS) was included as an adjuvant there was a small, but significant, increase in the rate of diffusion, and the total quantity of drug absorbed was promoted by 65% (fig 2). This SLS- induced increase in steady state flux (0.33 vs 0.54 $ugcm^{-2}hr^{-1}$) was accompanied by a significant reduction in the residual tissue levels of drug after the 4 hours (control - 18.8 ± 2.1% : SLS - 3.0 ± 0.6%). Thus it may be concluded that the absorption enhancement of SLS had been effected by increasing the flux of drug through the tissue, rather than merely promoting diffusion into the tissue. Polar molecules like RX77368 tend to be absorbed via the inter-cellular tight junctions. This enhancement of penetration may thus be due to direct SLS action on these tight junctions or ion-pair formation which subsequently facilitates more extensive transcellular absorption.

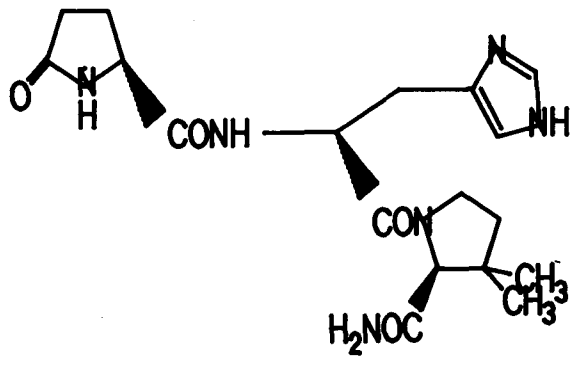

Fig 1 : The structure of tripeptide RX77368

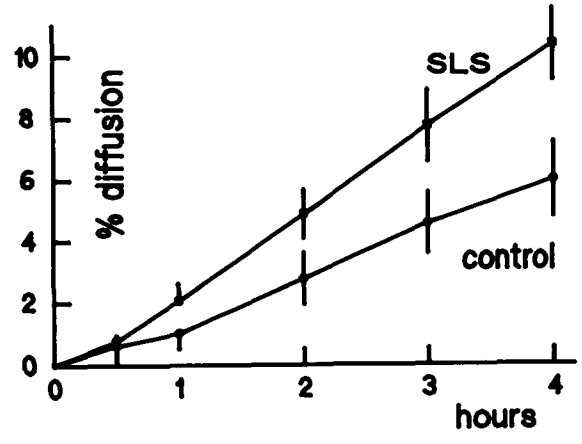

Fig 2 : Effects of SLS on 77368 diffusion across dekeratinised hairless mouse skin

Galey, W.R. et al (1976) J.Invest.Dermatol. 67: 713-717