MECHANISM OF IN-VIVO DISSOLUTION OF SUBCUTANEOUS SUSPENSION FORMULATIONS

W.R. Vezin, Beecham Pharmaceuticals, Research Division,
Great Burgh, Yew Tree Bottom Road, Surrey. KT18 5XQ

Subcutaneous suspension formulations of slightly soluble substances, e.g. aluminium hydroxide and tyrosine, are used in depot long acting therapy, for example desensitisation vaccines (Talmage & Dixon, 1953 and Miller et al, 1976). Modification of in-vivo dissolution rates of subcutaneous depots has been carried out by reformulation and administration in a variety of Newtonian liquids (aqueous buffer, monohydric alcohol esters, triglycerides, paraffins) and gels.

Gelation can cause large increases in subcutaneous lifetimes, but a X10 range in dissolution mass rates may be obtained among suspensions of L - tyrosine in Newtonian liquids alone. A mathematical model of approximating the behaviour of injected depots to dissolving oblate ellipsoids is introduced to describe and predict mass rates of depot dissolution.

Single small volumes of L - tyrosine Newtonian liquid suspensions were observed after S.C. injection to form rapidly into single accreted masses of particles, resulting from separation and passage of suspending liquid into surrounding S.C. tissue. An accretion may be approximated in shape to an oblate ellipsoid $(x^2 + y^2)/a^2 + z^2/b^2 = 1$, where 2a is the equivalent diameter of the accretion in the horizontal plane measured from photographs of excised S.C. tissue and 2b is the thickness deduced from depot particle density. Such depots were observed to dissolve monolithically with mass rates depending upon equivalent ellipsoid depot surface area, determined by accretion size and mean horizontal extent (2a) which depend upon overall formulation rheology and carrier hydrophilicity/solubility. Equivalent linear isotropic depot dissolution rates appeared to vary very little with these parameters however, or with suspension particle size or carrier biodegradability: suspensions in slowly metabolisable oils occasionally degrade significantly more rapidly than equivalent aqueous formulations.

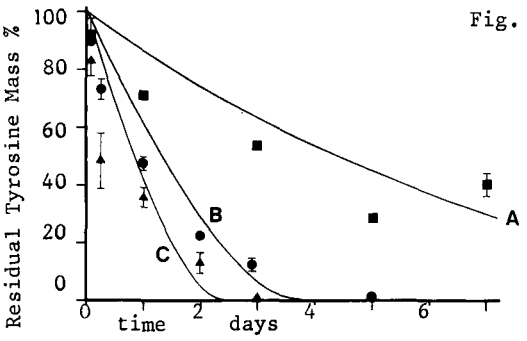

Fig. 1 in vivo S.C. tyrosine dissolution; 0.5ml injections, ■ 10% w/v tyrosine in light liquid paraffin, ● 4% in aqueous buffer and ▲ 4% in arachis oil; comparison with theoretical dissolution curves of corresponding mean ellipsoids A (a = b = 4.30), B (a = 5.55, b = 0.78) and C (a = 6.94; b = 0.495); for a single mean linear isotropic dissolution rate of 8.3 micrometres hour^{-1}. The specific surface of the suspended tyrosine is 9.92m^{2}g^{-1}.

Fig. 1 compares S.C. guinea-pig data of three formulations with theoretical dissolution curves of three mean oblate spheroids of a and b values corresponding to mean horizontal tissue dispersion, obtained with a single linear dissolution rate parameter. This suggests minimal influence of residual interstitial suspending liquid. Formulations in oil gels frequently yield lower linear dissolution rates, probably as the result of interstitial gel structure and non-accretion of tyrosine.

Miller, A.C.M.L. et al (1976) Acta Allergologica 31 : 35-43
Talmage, D.W., Dixon, F.J. (1953) J. Inf. Dis. 93 : 176-180

0022-3573/82/120006P-01$02.50/0