IN VITRO METHODS FOR ASSESSING THE AVAILABILITY OF GRISEOFULVIN FROM WATER-IMMISCIBLE VEHICLES

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An apparatus for simulating release of a drug from water-immiscible vehicles, such as those used in soft gelatin capsules, was described by Armstrong et al (1980), the apparatus being evaluated using a series of weak acids, which possessed appreciable water solubility. Possible alternative methods have been examined which might be suitable for use with non-electrolytes of much lower aqueous solubility, griseofulvin being selected as a model substance. A further aim was to reduce the amount of non-polar liquid from the 150ml used in the earlier technique to a volume closer to that used in a soft gelatin capsule.

Method A. A solution of griseofulvin in isopropyl myristate (20ml) was carefully poured on to the surface of an aqueous reservoir (200ml) stirred at 30 r.p.m. The absorption of the aqueous phase at 292 nm was continually monitored. Plots of $\ln(a_o/a_t)$ against time (t), where a_o and a_t are concentrations at zero time and time t respectively, were curvilinear, and typical of opposing migrations, in which back transfer from water to isopropyl myristate increases with time. Opposing reactions follow the equation

$$\ln(a_o-a_e)/(a_t-a_e) = (k_1 + k_{-1})\ t$$

where a_e is the equilibrium concentration and k_1 and k_{-1} are the forward and reverse rate constants (Frost & Pearson 1961). a_e was derived from the distribution coefficient between isopropyl myristate and water, and plots of $\ln(a_o - a_e)/(a_t - a_e)$ against t were rectilinear from which the forward rate constant could be calculated. The procedure is simple, but requires prior knowledge of the distribution coefficient.

Method B. Method A was not suitable for use with octanol, because the distribution coefficient was found to be concentration dependent, despite the absence of a proton donor in the solute. However, concentration-dependent distribution coefficients have been reported between octanol and water for testosterone esters, which also lack a proton donor (Medhizadeh 1980). The apparatus was therefore modified by dividing the upper layer into two parts, one containing an octanol solution of griseofulvin and the other pure octanol. The aqueous and pure octanol phases were monitored as before, and the concentration of griseofulvin in the third compartment calculated by difference. Sink conditions were maintained in the aqueous phase and the release from the octanol solution was first order. The procedure is not as simple as method A, but has the advantage that the distribution coefficient need not be known. The water-immiscible liquid must be a sufficiently good solvent for the maintenance of sink conditions in the water phase. Isopropyl myristate failed in this respect. Furthermore both upper reservoirs must contain the same solvent. Use of two different solvents will lead to contamination by transfer across the water phase.

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