USE OF A PHYSICAL MULTI-CELL MODEL TO CONFIRM THEORETICAL PREDICTIONS OF BIPHASIC STRUCTURE-ACTIVITY RELATIONSHIPS

J.C. Dearden, K.D. Patel, School of Pharmacy, Liverpool Polytechnic, Byrom Street, Liverpool L3 3AF, U.K.

The variation of biological potency within a congeneric series can often be quantified in terms of a quadratic equation in log (partition coefficient, P) (Hansch & Clayton, 1973). The decrease in biological potency at high lipophilicity may occur for various reasons (Hansch & Clayton, 1973), but, since it is such a widely-observed phenomenon, is likely to have one major cause. Yalkowsky and Flynn (1973) believe this cause to be the reduction of aqueous solubility as lipophilicity increases, whereas Penniston & others (1969) interpret such behaviour purely in terms of partitioning rates through a multiplicity of alternate aqueous and lipid phases. The mathematical model of Penniston & others (1969), based on multiple partitioning, indeed generated biphasic curves approximating to experimentally observed structure-activity relationships, but to our knowledge their model has not been tested physically. It could be argued, for example, that since partitioning rate does not increase indefinitely with partition coefficient (Lippold & Schneider, 1976), partitioning becomes diffusion-limited at high lipophilicity, and so the model fails. We constructed a physical model of eleven alternate aqueous and octanol cells by extending the three-cell model of Perrin (1967), in which a stirred floating layer of octanol links two adjacent stirred aqueous cells. Phase volume ratio was approximately 3:1, water:octanol. The final cell was made a total sink by having a continuous slow flow of octanol-saturated water through it. Single doses of drugs of varying lipophilicity (we used a series of five alkyl-substituted paracetamols) were placed in aqueous solution in cell 1, and the other cells sampled at various times. Movement of drug was very slow, several days being required for a single run. At various fixed times after dosage, log (concentration in n^{th} cell) was found to vary approximately parabolically with lipophilicity (see Fig. 1), thus confirming the validity of the theoretical model of Penniston & others (1969).

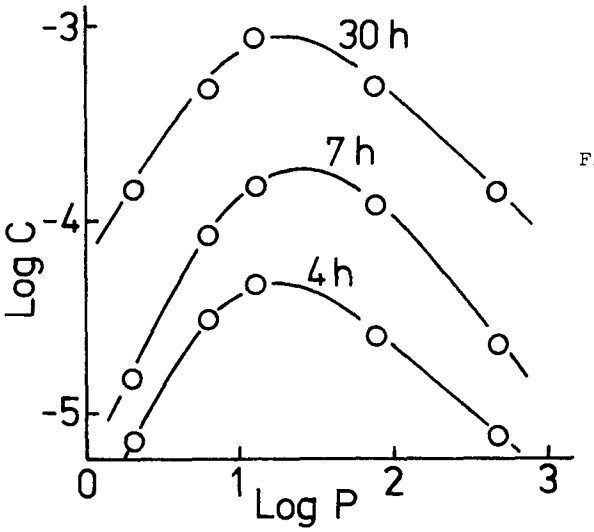

Fig. 1 Variation of drug concentration in cell 4 with lipophilicity, at various times following administration of 6.6×10^{-4} mole/litre in cell 1

Hansch, C. & Clayton, J.M. (1973). J.Pharm.Sci., 62, 1-21.
Lippold, B.C. & Schneider, G.F. (1976). Die Pharmazie, 31, 237-239.
Penniston, J.T., Beckett, L. & others (1969). Mol.Pharmacol., 5, 333-341.
Perrin, J. (1967). J.Pharm.Pharmac., 19, 25-31.
Yalkowsky, S.H. & Flynn, G.L. (1973). J.Pharm.Sci., 62, 210-217.