EFFECT OF LIPOPHILICITY OF IONISABLE DRUGS ON DEVIATIONS FROM EXPECTED PH-PARTITION BEHAVIOUR

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

On the assumption that the ionised fraction of an ionisable drug is insoluble in oily phases, the partition coefficient of the unionised species may be calculated from a knowledge of the apparent distribution coefficient at a pH giving a significant degree of ionisation, and of the pK of the solute. However, this assumption is probably incorrect; for example, 1-octanol contains, at saturation, about 27 mole % of water, and this water might be expected to accommodate some concentration of ionised species. This is possibly reflected in the fact that ionised species have finite, although low, lipophilicities; thus log P for salicylate ion is 3.09 lower than that for salicylic acid (Leo, Hansch & Elkins, 1971). We measured the pKa values of a series of ring-substituted aspirin derivatives, and determined their octanol-water distribution characteristics at pH values of 1, 4 and 6 using the AKUFVE instrument (Davis & Elson, 1974). The pKa values ranged from 2.8 to 4.5, so partition coefficients determined at pH 1 were effectively those of the unionised species. Partition coefficients at pH 1 were then calculated from partition measurements at pH 4 and 6, and compared with the experimentally determined values. The discrepancies between observed and calculated values correlated well (r = 0.88) with lipophilicity, as shown in Fig. 1, but showed no correlation with pKa; nor did inclusion of pKa in the regression equation with lipophilicity improve the correlation. This is not consistent with the error being due to partition of simple ionised species, which would be expected to be highly dependent on pKa. Furthermore, in order to explain the relationship shown in Fig. 1 one would have to make the rather doubtful assumption that the difference in log P values between unionised and ionised species decreased steadily as log P increased. We prefer to attribute the trend shown in Fig. 1 to ion-pair formation with buffer counter-ions (Moser, Jäkel & others, 1975), since the extraction of such ion-pairs into the non-aqueous phase should be directly related to their lipophilicity. That such a correlation as that shown in Fig. 1 is obtainable at all is a tribute to the precision with which partition coefficients can be measured on the AKUFVE instrument.

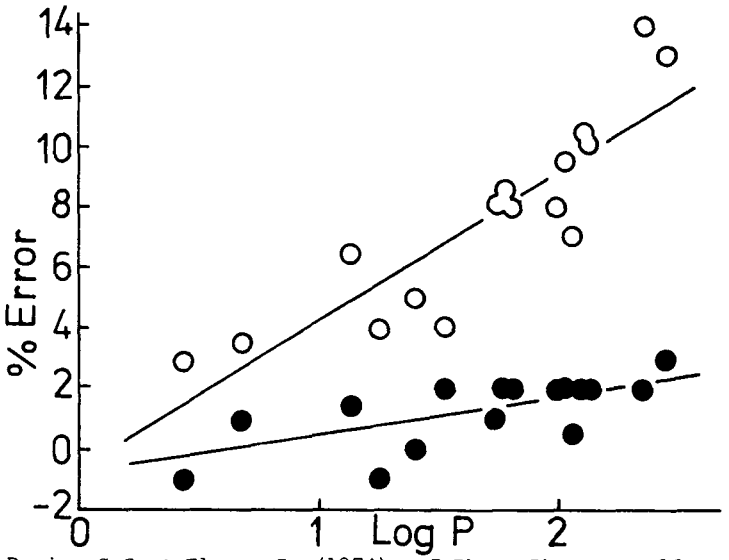

Fig.1. Error in calculation of partition coefficient at pH 1 from measurements at pH 4 (-●-) and 6 (-○-)

Davis, S.S. & Elson, G. (1974). J.Pharm.Pharmac., 26, Suppl., 90 P.
Leo, A., Hansch. C. & Elkins, D. (1971). Chem.Rev., 71, 525-616.
Moser, P., Jäkel, K. & others (1975). Eur.J.Med.Chem., 10, 613-617.