J. Pharm. Pharmacol. 1990, 42: 144
Communicated October 2, 1989

Letter to the Editor

An improved method for the determination of distribution coefficients

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Lipophilicity is a property of drugs that has been related to pharmacokinetics (Seydel & Schaper 1982), metabolism (Hansch 1972) and biological activity. This property can be measured by determination of the distribution of drug between an organic solvent, usually n-octanol, and a buffered aqueous phase. The distribution coefficient (D) is defined as the ratio of the concentration of compound in the organic phase to the concentration of both ionized and unionized species in the aqueous phase at a given pH (Scherrer & Howard 1977). In contrast, the partition coefficient (P) refers to the ratio of unionized compound in each phase and can be calculated using the MedChem computer program (Chou & Jurs 1979; Leo 1987).

The correlation between log D, log P and metabolic processes has been discussed by Manners et al (1988) and emphasises the value of log D measurements particularly where metabolism alters the ionisation of a drug.

The traditional shake flask method for measuring distribution (Leo et al 1971) has been modified to minimize the amount of compound required (1–2 mg) by employing HPLC to determine the concentration of the compound in the octanol and buffer phases. This procedure is particularly suitable for rapid evaluation of compounds since it reduces errors due to any impurities present. These errors can be serious when high log D values are measured using the shake flask technique, if the impurities have a low log D value.

Compound (0·5–2 mg) was dissolved in 2 mL octanol (or buffer if more soluble in aqueous solution) in a 10 mL screw-neck tube. After addition of 2 mL buffer (or octanol) the phases were mixed for 1 h and then centrifuged. One mL of the upper octanol phase was collected and also, after discarding octanol at the interface, 1 mL of buffer.

Each phase was analysed for compound by HPLC using a reverse phase Spherisorb octyl column (12·5 × 0·5 cm) with a mobile phase of methanol–ammonium phosphate 0·01M, pH 7. The proportions of methanol and buffer were adjusted for each compound to give a capacity factor in the range 2–8. Volumes up to 10 μL of the octanol phase and 1 mL of the buffer phase could be injected.

The distribution coefficient (D) was calculated from the ratio of peak area for compound/volume injected in octanol to peak area for compound/volume injected in buffer.

The method was validated using a range of drugs with log D values from −2 to 4 (Table 1). The results indicate the reliable performance of the method over a range of 10^6 in terms of partitioning behaviour.

Table 1. Comparison of literature values of log D with values given by the modified method.

Compound	Literature values of log D(pH 7·4) (from the MEDCHEM program) Mean and range	Measured log D (mean of two determinations)
Atenolol	−1·89 (−1·74 to −2·00, n = 5)	−2·0
Sulfanilamide	−0·76	−0·7
Acebutolol	−0·22 (−0·17 to −0·28, n = 3)	−0·31
Propranolol	1·21 (0·93 to 1·41, n = 6)	1·20
Quinidine	2·09 (2·07 to 2·11, n = 2)	2·14
Thymol	3·30	3·27
Chlorpromazine	3·28 (3·15 to 3·50, n = 4)	3·46
Phenothiazine	4·15	4·30

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