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Distribution coefficients of atenolol and sotalol

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The distribution coefficient (D) of atenolol is lower than that of sotalol, despite the latter's lower partition coefficient (P). Since D is the relevant quantity under physiological conditions, it is re-established that atenolol is in practice the more hydrophilic. Because of the common confusion between P and D which this case exemplifies, the relation between them is set out.

The tissue distribution of β-adrenoceptor antagonists (β-blockers) is markedly influenced by their physicochemical properties, especially their relative solubility in organic solvents. β-Blockers which are relatively hydrophilic are considered to possess clinically relevant advantages, of which low penetration of the cns is the most important (Cruickshank 1980; Neil-Dwyer et al 1981). The more lipophilic β-blockers are associated with a higher incidence of central nervous system side effects (Westerlund 1982).

The assessment of the degree of hydrophilicity of β-blockers is complex. Recently, Woods & Robinson (1981) showed that atenolol was the most hydrophilic of a series of clinically available β-blockers whilst Cruickshank, in an earlier publication, indicated that sotalol was more hydrophilic.

To clarify these apparently conflicting results, we have re-examined our data and carried out further experiments which are now reported.

Theoretical considerations

In the Cruickshank paper, the data were reported as *partition coefficients*, whilst Woods and Robinson determined the *distribution coefficients* of a series of β-blockers. The term partition coefficient, P, is related to the chemical characterization of an organic molecule and is strictly defined as the ratio of concentration for the *same molecular species* between two liquid phases at equilibrium (Leo et al 1971) i.e. $P = [B]_{org}/[B]_{aq}$ where $[B]_{org}$ and $[B]_{aq}$ represent the concentrations of the species B in the organic (or lipid) and aqueous phases respectively. For compounds that do not ionize, no ambiguities arise in applying results from this in-vitro system to biological systems.

In contrast, the term distribution coefficient is more applicable to biological systems because it takes into account the possible influence of variation in pH and temperature. This is especially important if the organic species becomes ionized in solution. If we suppose that B is a base that can ionize in water to give a second species, the cation BH^+, which is what happens with the beta blockers, a double equilibrium is set up;

$$[BH^+]_{aq} \overset{K_a}{\rightleftharpoons} [B]_{aq} \overset{P}{\rightleftharpoons} [B]_{org} \quad \text{(i)}$$

where K_a is the ionization constant (generally expressed, as is P, in logarithmic form). To the extent that B ionizes to give BH^+, the *effective* partition coefficient will fall. This effective partition coefficient is commonly known as the distribution coefficient D, defined by $D = [B]_{org}/([B]_{aq} + [BH^+]_{aq})$. Thus D is a pH-dependent quantity having a maximum value of P. The logarithmic forms are quantitatively related by equation (ii):

$$\log D = \log P - \log [1 + \text{antilog}\,(pK_a - pH)] \quad \text{(ii)}$$

This equation can be used to calculate D from P at any pH, given that pK_a is known.

Results

The calculated and experimentally determined partition and distribution coefficients for atenolol and sotalol are shown in Table 1. The first two columns show their log P and pK_a values as determined by ourselves at 25 °C. These are then used to calculate D at 25 °C by means of equation (ii). The fourth and fifth columns give the experimental D values at 37 °C, as determined by Woods & Robinson (1981) and ourselves. These latter are in satisfactory agreement with each other and consistent with the results calculated from data obtained at 25 °C bearing in mind the expected fall in pK_a with rising temperature (Albert & Serjeant 1962) so that, again from equation (ii), D is expected to rise.

The higher value of D for sotalol than for atenolol despite its lower P (or log P) is a consequence of its lower pK_a; in this respect sotalol is an untypical β-blocker.

On the pH-partition hypothesis (Hogben et al 1957),

Table 1. Partitioning data on atenolol and sotalol.

Drug	log P (25 °C)	pK_a (25 °C)	Distribution coefficients (D): pH 7·4 and 25 °C (calc.)[a]	pH 7·4 and 37 °C (this work)	pH 7·4 and 37 °C (lit.)[b]
Atenolol	0·23	9·55	0·012	0·018	0·015
Sotalol	−0·79	8·37	0·016	0·030	0·039

[a] From equation (ii).
[b] Woods & Robinson 1981.

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D rather than P is expected to be the quantity relevant to the relative rates and equilibria of partitioning for a series of agents under physiological conditions, and this point has been re-emphasized in the context of narcotics and narcotic antagonists (Kaufman et al 1975). It follows therefore that the *pharmacologically effective* partition coefficient of atenolol is about half that of sotalol.

In conclusion, under physiological conditions i.e. pH 7·4 and 37·0 °C, atenolol has an *effective partition coefficient*, i.e. distribution coefficient, which is about half that of sotalol. On the basis that the distribution coefficient is the determinant of tissue distribution in-vivo, atenolol may be regarded as the most hydrophilic of the clinically available β-blockers.

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The evaluation of an automatic system for filling liquids into hard gelatin capsules

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A system is described in which an intermittent motion powder filling capsule machine is modified to fill liquids into hard gelatin capsules suitable for pilot scale or small production batches. The system is shown to be suitable for filling materials covering a wide range of viscosities and to give excellent fill weight uniformity which is largely independent of operating conditions. The process is clean and trouble-free.

The advantages of filling hot melt or thixotropic liquids into hard gelatin capsule shells in which they solidify to form a stable solid plug, have been well documented in recent years. These include low content uniformity variation, reduced dust generation giving rise to reduced cross contamination hazards, controlled dissolution rate using solid solution or slow release systems, the ability to process low melting point or liquid drugs and the possibility of in-house formulation development and manufacture (Walker et al 1980a, b; Cuiné & Francois 1981).

Equipment is available to manufacture very small batches of liquid filled capsules by hand and at the other extreme very large batches can be processed using purpose-built liquid fill capsule machines. There is currently no machine available for the manufacture of pilot scale and small production batches. We therefore describe the modification and evaluation of a Zanasi LZ64 (ACM Machinery Ltd.) automatic, intermittent motion powder filling machine to enable the manufacture of 4400 liquid filled capsules per hour.

Equipment. The modifications to the capsule filling machine comprise a series of elements now described; (the sequence of operation is described and the system is illustrated schematically in Fig. 1).

Liquid filling system. The powder hopper and dosator tubes are replaced by a heated stainless steel reservoir and liquid metering pump (Hibar Model HBD-1A, Höfliger, West Germany). The pneumatically operated pump can deliver volumes of 0·05 to 1·5 ml of liquid at a rate of up to 150 doses per minute with infinitely variable dose and temperature control over the range ambient to 100 °C. The reservoir and dosing nozzle are maintained above ambient temperature by heating tape (Hot Foil Ltd. U.K.) and a heating block respectively and thermostatic control is achieved by thermistors (R.S. Components Ltd.).

Capsule detection. A system was developed to disable the pump in the absence of a capsule shell at the filling

Table 1. Fill weight uniformity using the liquid fill system.

Trial	Duration min	Total Wt* (mg) mean	range	c.v. %	Fill wt mean mg
I	100	328	318–338	0·71	254
II	120	324	317–339	0·76	250

* Size 1 capsule shells, mean weight 74 mg c.v. 3·2%.

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