Partition and distribution coefficients

Absorption of drugs

There are a number of ways that drugs are absorbed,[1] but the most common route is passive transport (diffusion). Passive transport does not require an input of energy.

A cell membrane has a central layer that is lipophilic (hydrophobic). The IUPAC definition of lipophilic is:

'Having an affinity for fat and high lipid solubility: a physicochemical property which describes a partitioning equilibrium of solute molecules between water and an immiscible organic solvent, favouring the latter, and which correlates with bioaccumulation.'

The relative solubility of a substance in water and an organic solvent (water-immiscible) is a measure of lipophilicity.

Experiments have shown that lipophilicity is an important property of a drug that influences passive transport across cell membranes. A drug molecule needs to be sufficiently lipophilic that it enters the lipid core of a cell membrane, but not so lipophilic that it is held in that core and does not move into the cell.

Figure1 The shake flask method.

Partition coefficient

In drug discovery and development, lipophilicity is usually expressed by the partition between water and octan-1-ol.

The partition coefficient, *P*, of a drug is given by

$$P = \frac{[drug]_{octan-1-ol}}{[drug]_{water}}$$

where

$[drug]_{octan-1-ol}$ = concentration of drug in octan-1-ol

$[drug]_{water}$ = concentration of drug in water

A sample of the drug is shaken with a mixture of octan-1-ol and water and its concentration in each layer is determined.

It is usual to give the log*P* value (the logarithm to the base 10 of the partition coefficient). Sometimes a value is calculated - from knowledge of the molecular structure - rather that determined experimentally. These values are denoted by using clog*P*.

The drug molecule must be unionised in aqueous solution.

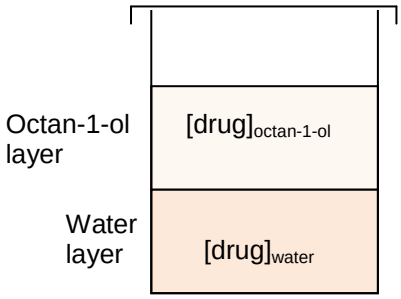


Figure 2 Partition between octan-1-ol and water.

Distribution coefficient

Most drugs, however, are weak acids or weak bases that partially ionise when dissolved in water.[2]

$$HA + H_2O \leftrightarrow H_3O^+ + A^-$$

HA = acid (the drug molecule); H_2O = base

A^- = conjugate base (the drug anion); H_3O^+ = conjugate acid

$$B + H_2O \leftrightarrow BH^+ + OH^-$$

B = base (the drug molecule); H_2O = acid

OH^- = conjugate base (the drug anion); BH^+ = conjugate acid

[1] See *Pharmacokinetic processes: absorption.*
[2] See *Ionisation of drug molecules* and *Drugs and acid dissociation constants.*

The pH of the aqueous solution affects the proportion of molecular and ionised forms of the drug.

The distribution constant, *D*, of a drug is given by:

$$D = \frac{[drug\ molecule]_{octan-1-ol}}{[drug\ molecule]_{water} + [drug\ ion]_{water}}$$

where

$[drug\ molecule]_{octan\text{-}1\text{-}ol}$ = concentration of drug in its molecular form in octan-1-ol

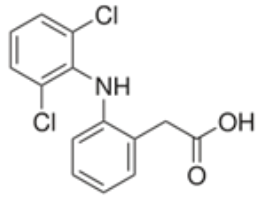
$[drug\ molecule]_{water}$ = concentration of drug in its molecular form in water

$[drug\ ion]_{water}$ = concentration of drug in its ionised form in water

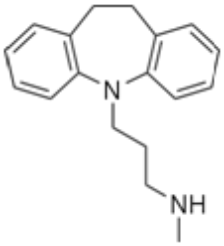
The distribution constant is pH dependent and the term log*D* is used to reflect the pH dependent lipophilicity of a drug.

The lower the pH of an aqueous solution, the further to the left is the position of equilibrium, i.e. increasing $[drug\ molecule]_{water}$ and decreasing $[drug\ ion]_{water}$.

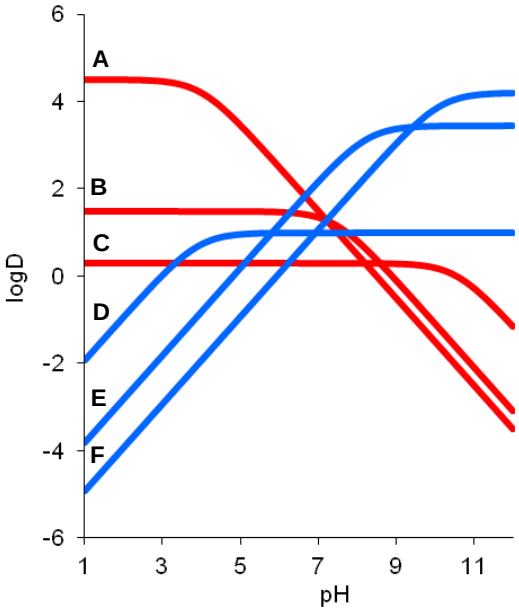
Below a certain pH, $[drug\ ion]_{water}$ becomes close to zero. This is shown in the graphs in figure 3. For each compound the horizontal part of the curve shows when log*D* = log*P*, in other words the range when distribution is not pH dependent.



Diclofenac (**A**) is a non-steroidal anti-inflammatory drug



Desipramine (F) is an antidepressant



A: Diclofenac
pK_a = 3.99
B: Phenobarbitol
pK_a = 7.43
C: Nifuroxide
pK_a = 10.56
D: Triamterene
pK_a = 3.92
E: Diphenhydramine
pK_a = 8.26
F: Desipramine
pK_a = 10.14

Figure 3 Graphs of log*D* against pH for six drugs. Those shown in **red** are acids. Those in **blue** are bases. (Data courtesy of Sirius Analytical).

Finding out

What apparatus is used in the shake-flask method for determining distribution coefficients and how is the test carried out?

What are the modern alternatives to the shake-flask method?