Dissolution and solubility

Dissolution

Most medicinal drugs are formulated into tablets, capsules or other forms of medicine.

Formulating a medicine means mixing the medicinal drug with other ingredients (called excipients) according to a prescribed recipe (the formulation). These ingredients have a number of purposes in a tablet, for example, they might help bind the tablet together, control the rate of release of the drug and improve the taste of the tablet.

Figure 1 Aspirin tablets slowly disintegrate in water. They are usually swallowed whole.

Figure 2 Capsules contain tiny particles of a drug. Their shape and smooth polymeric coating means many people find them easier to swallow than tablets. In the body, the coating dissolves slowly, releasing the drug.

Dissolution of a tablet involves its disintegration into smaller and smaller particles from which the medicinal drug is released more and more rapidly.

The speed at which a medicinal drug is released from a tablet or capsule and dissolves in solutions that mimic fluids in the GI tract is an increasingly important measurement. Knowledge of this rate of dissolution contributes to the formulation, development and regulatory approval of medicines. It is also important for quality control, checking that the tablets from a production run have the required characteristics.

The process of dissolution followed by absorption determines, in part, the bioavailability of the drug. The rate of dissolution can be determined *in vivo* by taking samples of a person's plasma or urine and measuring the drug concentration in them.

However, this is not appropriate for routine measurements on the vast numbers of compounds investigated during drug discovery and development. Instead, *in vitro* tests are used. Fluids in the body are simulated and dissolution experiments carried out in laboratory glassware. Conditions for these tests are carefully defined in pharmacopoeias.

Figure 3 Dispersible ('soluble') aspirin is formulated so that tablets effervesce when put it water.

Dissolution of a tablet depends on:

- the size of the granules of medicinal drug;
- the structure of the tablets and the nature of the excipients used in the formulation;
- the pH of fluids in the GI tract.

It also depends on temperature, but since body temperature is always 37 °C (or very close) temperature is not a factor in this situation.

Solubility and absorption

To be absorbed across cell membranes or pass through intercellular pores a medicinal drug must be in solution. The rate at which a drug gets into solution is important, but if its solubility is low its pharmacokinetic and pharmacodynamic properties might be adversely affected.

It has been said that low solubility is top of the list of undesirable properties of a potential medicinal drug. So being able to measure solubility and, if necessary, modify a compound to alter its solubility without affecting its therapeutic properties is important.

The solubility of a compound is the quantity present in a saturated solution in contact with an excess of undissolved solid. This is **equilibrium solubility**. Traditionally, it is measured by the shake-flask method. Excess compound is shaken with a solvent until a saturated solution is produced with an excess of the solid compound present. It is an accurate but very time-consuming method.

Pharmacologists also measure **kinetic solubility**. Precipitation is induced, for example, by changing the polarity of the solvent and the concentration at which a precipitate first appears is measured. It can be defined as the solubility at the time when an induced precipitate forms. So, for example, a solution might be slowly evaporated until a solid begins to precipitate.

Factors affecting solubility

So why are some compounds more soluble than others? Solubility is often said to be a physical change, but it does involve chemical bonds being broken and new ones formed.

Like all change, the dissolution of a solid in a solvent is governed by:

- thermodynamic factors;
- kinetics factors.

Thermodynamic factors are summarised by the equation:

$$\Delta G = \Delta H - T\Delta S$$

where ΔG = change in free energy / J

ΔH = change in enthalpy / J

ΔS = change in entropy / JK^{-1}

T = temperature / K

The more negative ΔG, the more thermodynamically feasible the change.

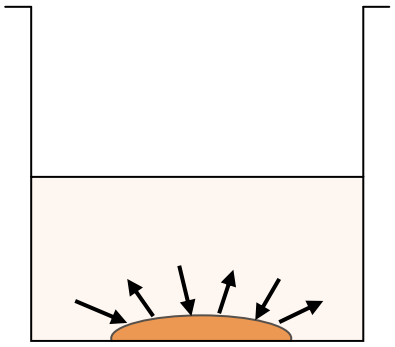

Figure 4 Solute particles in a saturated solution are in dynamic equilibrium with solute particles in the solid.

In any dissolution, the entropy of the system increases (ΔS is positive) and so is a driver for change.

The stronger the bonds in a solution compared with the bonds in the solvent and the solid, the more negative the enthalpy change (ΔH). This is the other thermodynamic driver for change.

The activation energy of the dissolution process is the kinetic barrier to a solid dissolving.

However, the process is rather more complicated because it happens at the surface of the solid, and the chemistry of the surface of a solid differs to that of the bulk solid.

Nonetheless the ionic or molecular structures of solids and the solvated species they form in solution provide a valuable insight into solubility.

Finding out

What is the difference between disintegration and dissolution? Why is disintegration important?

Design a method to determine the solubility of a drug in the stomach. Two questions to answer first: What is the pH of fluid in the stomach? What is body temperature?