Ionisation of drug molecules

Drug liberation, absorption and distribution

The first three stages of the pharmacokinetic process are:

- Liberation[1] – release of the medicinal drug from a formulated medicine.
- Absorption[2] – movement of the liberated drug into the bloodstream.
- Distribution[3] – passage of the drug from the bloodstream to body tissues and organs.

As a rule of thumb, molecular compounds are less soluble in water than in non-polar solvents, while ionic compounds are more soluble in water than in non-polar solvents.

In the body there are two distinct environments. One, such as blood plasma, is aqueous and so ionic compounds are more likely to be soluble in blood than are molecular compounds.

The other is cell membrane which is mainly composed of non-polar lipids (phospholipids, glycolipids and cholesterol). The central part of the membrane, therefore, consists mainly of long chain hydrocarbons and so molecular compounds are more likely to be soluble in cell membrane than are ionic compounds.

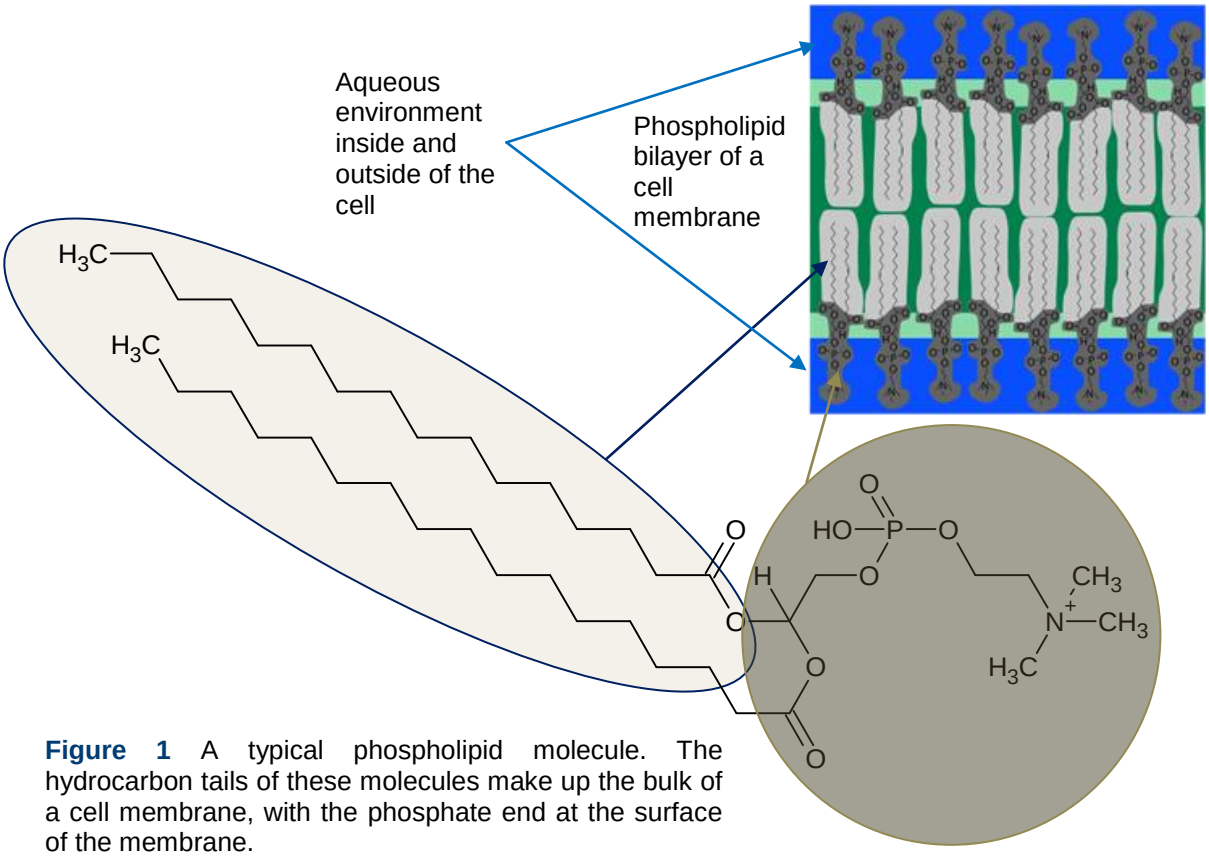


Figure 1 A typical phospholipid molecule. The hydrocarbon tails of these molecules make up the bulk of a cell membrane, with the phosphate end at the surface of the membrane.

An effective drug needs to be sufficiently soluble in water to dissolve in blood plasma and be carried around the body while also being sufficiently soluble in non-polar lipids to pass through cell membranes into cells.

[1] *Pharmacokinetic processes: liberation.*
[2] *Pharmacokinetic processes: absorption.*
[3] *Pharmacokinetic processes: distribution.*

Ionisation

Most drug molecules ionise in aqueous solution to give weakly acidic or basic solutions.

Naproxen is a non-steroidal anti-inflammatory drug (NSAID). It is used to relieve pain and inflammation in, for example, rheumatic disease, sprains, strains, backache, gout, and period (menstrual) pain.

A naproxen molecule has a carboxylic group and so is a weak acid. It ionises in water to give an equilibrium solution that contains a mixture of unionised molecules, carboxylate ions and hydroxonium ions (figure 2).

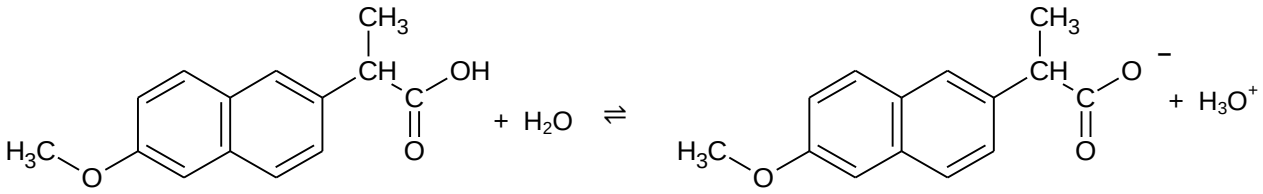
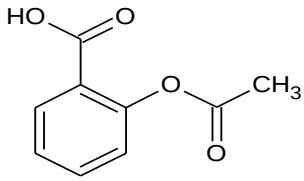
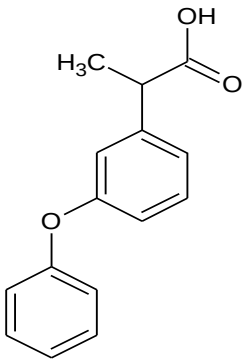


Figure 2 The dissociation of naproxen in aqueous solution.

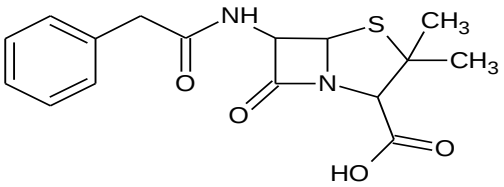
Fenoprofen and penicillin G (benzylpenicillin) are drug molecules that also contain carboxylic acid groups. Both compounds partially ionise in aqueous solution.



Aspirin



Fenoprofen



Penicillin G

Figure 3 These three medicinal drugs also form weakly acidic solutions in water.

The general reaction may be represented by

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

where,

HA = acid (the drug molecule);

H_2O = base;

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

H_3O^+ = conjugate acid.

Diphenhydramine is a first generation antihistamine used to treat allergic symptoms such as hay fever though it does have as sedating effect. More recently developed antihistamines are not sedating. The sedating properties of diphenhydramine explain its use to treat insomnia and travel sickness (cars, boats and planes).

A diphenhydramine molecule has an amine group and so is a weak base. It ionises in water to give an equilibrium solution that contains a mixture of unionised molecules, quaternary ammonium ions and hydroxide ions (figure 4).

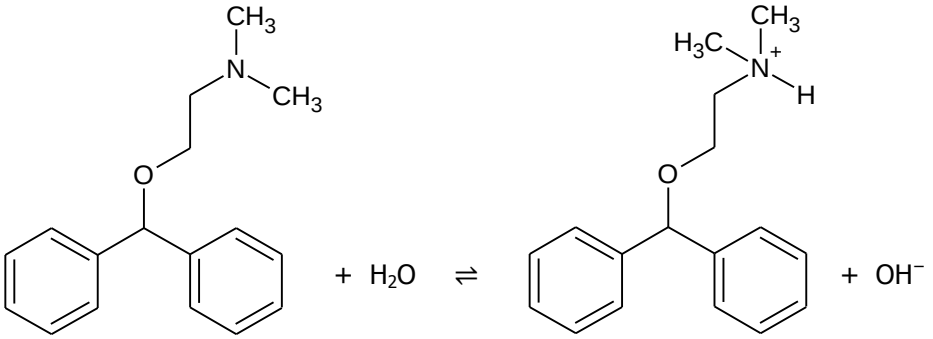


Figure 4 The ionisation of diphenhydramine in water.

The general reaction may be represented by

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

where,

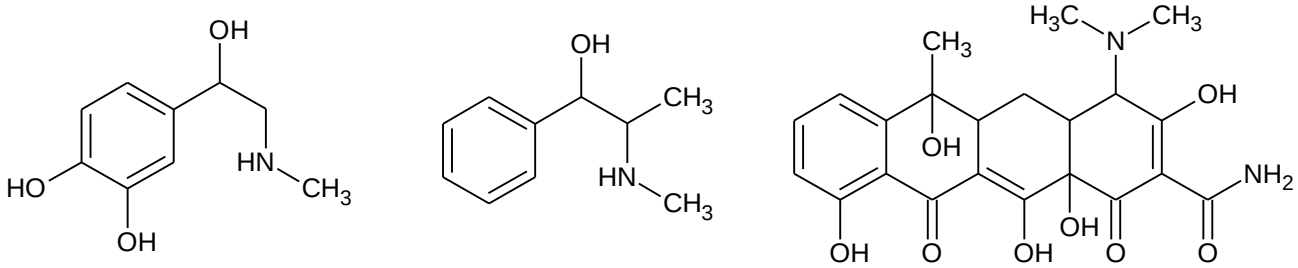
B = base (the drug molecule);

H_2O = acid;

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

BH^+ = conjugate acid.

Other drugs which are bases include adrenaline, ephedrine, atropine and tetracycline.



Adrenaline Ephedrine Tetracycline

Figure 5 These three medicinal drugs form weakly basic solutions in water.

Finding out

The pH of aqueous solutions in which a drug is dissolved determines the form in which the drug is present – molecule or ion.

This is particularly important for drugs taken orally as pH varies through the gastrointestinal tract.

What are the pH values for fluids in different sections of the gastrointestinal tract?

Based on this information, where in the gastrointestinal tract will the following drugs be absorbed from the bloodstream most quickly? (a) aspirin, (b) ephedrine.