

Pharmacokinetics

Taking tablets and capsules

Many drugs are formulated as tablets or capsules to be taken orally.

To be effective a medicinal drug taken by mouth should:

- dissolve and be stable in solutions with differing pH values; the pH of liquids in the gastrointestinal (GI) tract, for example, ranges from 1.5 to 8;
- be resistant to bacteria in the intestine and resistant to metabolism in the liver;
- avoid active transport to bile and not be excreted by kidneys;
- be able to pass through cell membranes; the most common mechanism, is passive transport;
- move into the target organ;
- bind to a receptor site, often an enzyme or other protein molecule.

How well a drug meets these requirements depends on its physical and chemical properties. These properties determine the pharmacokinetic processes that a drug undergoes in the body.

The physiochemical properties of drugs administered in other ways, such as inhalation or injection, are equally important. The effectiveness of all drugs is linked strongly to their physiochemical properties.



Figure 1 A drug taken in the form of a tablet or capsule must reach its target safely.

Pharmacokinetic processes

The pharmacokinetic processes that follow a drug dosage being administered is often described as a series of input processes and output processes.

Input processes

- Liberation
Release of the drug from its administered form.
- Absorption
The movement of a drug from where it is liberated into the bloodstream.

Note: The term bioavailability is often used to describe the rate and extent of drug input. Drugs administered intravenously have essentially 100% bioavailability.

Output processes

- Distribution
The process by which drug passes from the bloodstream to body tissues and organs.
- Metabolism
The chemical reactions that change drugs into compounds which are easier to eliminate.
- Excretion
The elimination of unchanged drug or metabolite from the body.

The processes usually follow this sequence, but often overlap. All five processes may even occur simultaneously. A sustained release (SR) tablet may still be liberating the medicinal drug as some of the drug liberated earlier is being eliminated. Collectively, these processes are given the acronym LADME.

Toxicity

Nearly all useful medicinal drugs produce unwanted effects in the body. This is almost inevitable given the complexity of the human body. Some produce potentially dangerous effects.

The potential a drug has to cause harm is called its toxicity. Adding toxicity to LADME gives the acronym LADMET.

While unwanted side-effects are common, the harmful side-effects of a medicinal drug should be minimal. Doctors compare the benefits and risks when deciding whether or not to prescribe a drug.

Chemical and physical properties affect pharmacokinetic processes

Pharmacokinetic processes depend on the chemical and physical properties of a medicinal drug.

Properties of particular importance include:

- solubility and rate of dissolution of the drug at pH values found in the human body (important for drugs taken orally); this can be affected by crystal type and size and by the pH of the solution;
- the lipophilicity (fat-solubility) of the drug molecules; the tendency of the drug to dissolve in non-polar media rather than aqueous solutions, and their permeability across the gastrointestinal tract;
- the tendency for the drug molecules to ionise (measured by its acid dissociation constant); movement through lipid membranes, where passive diffusion is most common and, therefore, neutral molecules pass more quickly than charged ions;
- the chemical stability of the drug, both when stored and when in conditions found in the human body (resistance to changes in temperature and to reactions with water, air and solutions of different pH).

Modern advances

Advances in synthetic organic chemistry techniques, such as combinatorial synthesis and parallel synthesis, have enabled chemists to produce large libraries of related compounds in their search for a lead compound. Similarly, advances in screening techniques have enabled the biological activity of these compounds to be assessed quickly. The result is that the discovery of compounds with good biological activity and strong affinity for receptor sites has become quicker. As a result, the focus has shifted to early measurement of properties that affect the pharmacokinetic processes.

Finding out

How are solubility, rate of dissolution, lipophilicity and acid dissociation constants determined?



Figure 2 Using drugs to treat cancer (chemotherapy) can cause unwanted side-effects such as hair loss.