Chapter 15: Medicinal chemistry – fast facts

D.1 Pharmaceutical products and drug action

Medicines and drugs have a variety of different effects on the functioning of the body.

- Drugs can be administered in different ways : orally, inhalation, absorption through skin, suppositories, eye or ear drops, or by injection.
- Bioavailability refers to the fraction of an administered drug that reaches its target in the body. Intravenous administration gives a bioavailability of 100%. Drugs taken orally have a lower bioavailability due to the first-pass effect. Bioavailability is influenced by the solubility of the drug in water and in lipid, and by functional groups in the drug which influence polarity and so solubility.
- Side-effects refer to unintended physiological effects of drugs in the body. They can be beneficial, harmless, or adverse – so must be monitored.
- Tolerance occurs when repeated doses of a drug result in smaller physiological effects.
- Addiction occurs when the dependency on a drug leads to withdrawal symptoms if it is withheld.
- Dosage refers to the amount of a drug taken over an interval of time.
- The therapeutic window is the range of concentrations of a drug in the blood between its therapeutic and toxic levels.
- The therapeutic window is quantified as the therapeutic index. This is the ratio of the lethal dose (in animals, LD50) or toxic dose (in humans, TD50), divided by the minimum effective dose (ED50).
- Drugs with a low therapeutic index have a low margin of safety, so dosage here is crucial. Animal and human tests of drug dosages should be kept to a minimum.
- Understanding drug–receptor interactions has contributed largely to rational drug design. Drug development depends on identifying the need and identifying a suitable target in the body. The process is slow and costly, though optimized by combinatorial chemistry and the synthesis of analogues.
- Drug trials for potential drugs involve animals and humans in three phases. Each phase involves larger numbers of patients. Phase III uses double-blind trials to test the effectiveness of the drug against a placebo.

D.2 Aspirin and penicillin

Natural products with useful medicinal properties can be chemically altered to produce more potent and safe medicines.

- Aspirin is a mild analgesic that acts to block the pain stimulus at source. It also acts as an anticoagulant in the blood. It has a synergistic effect with alcohol, which can cause stomach bleeding.
- Aspirin can be synthesized from salicylic acid in an esterification reaction. The reaction uses ethanoyl chloride and concentrated sulfuric acid or phosphoric acid.
- Purification of aspirin involves recrystallization, which causes it to crystallize from a hot saturated solution of ethanol during cooling, while the impurities stay in the solution.
- The aspirin product can be characterized by melting point determination and by IR spectroscopy. Aspirin gives distinct peaks due to its –COOH and ester groups.
- Modification of aspirin to soluble form involves reacting it with an alkali to form an ionic salt.

- Penicillin is an antibiotic that was first extracted from the mould *Penicillium* and characterized using X-ray crystallography.
- Penicillin contains a beta-lactam ring in which the carbon atoms are under bond strain. Breakage of these bonds allows the antibiotic to inhibit the bacterial enzyme transpeptidase that is essential in the synthesis of bacterial cell walls. This kills the bacteria.
- The side-chains in penicillin have been modified to allow the drug to be administered orally, as this modification prevents its breakdown in the stomach.
- Many bacteria have become resistant by developing beta-lactamase enzymes which break the beta-lactam ring. Different forms of penicillin, methicillin and oxacillin, have modified side-chains which prevent the binding of the beta-lactamase enzyme.
- Response to antibiotic resistance must include monitoring of over-prescription by medical practitioners and greater patient compliance in completing a dose.

D.3 Opiates

Potent medical drugs prepared by chemical modification of natural products can be addictive and become substances of abuse.

- Opiates are strong analgesics, derived from poppy seeds, which act to reduce the perception of pain in the brain. They bind to specific opioid receptors in the brain.
- The blood–brain barrier is largely lipid and so is crossed more easily by non-polar drug molecules.
- The opiates cause side-effects such as constipation, which are not serious, but they also have narcotic effects and are highly addictive. Addiction to diamorphine (heroin) is a very serious condition and is often linked to other social problems due to the dependence.
- Morphine is converted into codeine by methylation and into diamorphine by esterification. Diamorphine is able to cross the blood–brain barrier more quickly and so is the fastest acting opioid. In terms of their analgesic properties, side-effects and narcotic effects:

  codeine < morphine < diamorphine

D.4 pH regulation of the stomach

Excess stomach acid is a common problem that can be alleviated by compounds that increase the stomach pH by neutralizing or reducing its secretion.

- HCl is produced by parietal cells in the gastric glands of the stomach.
- Excess acid from the stomach causes dyspepsia and can lead to ulceration.
- There are two types of drugs that prevent the production of excess acid.
  - i Drugs that block the histamine-H_2 interaction in the gastric glands: these drugs compete with histamine for binding at the receptors. They include ranitidine.
  - ii Drugs that inhibit the proton pump that parietal cells use to pump H^+ ions into the stomach lumen. They include omeprazole and esomeprazole.
- Antacids are weak bases that act to neutralize excess stomach acid. They include calcium, magnesium, and aluminium hydroxides and sodium carbonate and hydrogencarbonate. The stoichiometry of these reactions determines the amount of HCl that can be neutralized by each antacid.

- Cells contain buffer solutions that keep the pH relatively constant on the addition of small amounts of acid or base.
- The pH of a buffer solution can be determined from the pK_a or pK_b of the parent acid/base and by the relative concentrations of acid/base and salt.
- The Henderson–Hasselbalch equation is: $\text{pH} = \text{p}K_a + \log\frac{[\text{salt}]}{[\text{base}]}$

D.5 Antiviral medications

Antiviral medications have recently been developed for some viral infections while others are still being researched.

- Viruses lack a cell structure and so are more difficult to treat in the body than bacteria. Viruses consist only of genetic material (DNA or RNA) and protein. They synthesize other components inside the host cell.
- Antiviral drugs target specific viral infections. They work by causing changes to the cell membrane which prevent the entry of viruses, altering the cell's DNA so it cannot be used by the virus, or blocking enzyme activity to prevent viral multiplication.
- Oseltamivir and zanamivir are antivirals for flu that inhibit the enzyme neuraminidase, which allows new viral particles to escape from the host cell and cause infection. They must be taken immediately as symptoms appear or the viral infection will already have spread too far.
- Oseltamivir and zanamivir have similar structures, and act as competitive inhibitors with neuraminidase as their structures are similar to sialic acid, its normal substrate.
- HIV infection, which can lead to AIDS, is particularly difficult to treat. The virus destroys cells in the immune system, mutates very rapidly, and can often lie dormant within cells for years. Anti-retrovirals target interactions between the virus and host cells, the enzyme reverse transcriptase, and the release of new viral particles.

D.7 Taxol: a chiral auxiliary case study

Chiral auxiliaries allow the production of individual enantiomers of chiral molecules.

- Taxol is derived from the bark of Pacific yew trees and is used to treat cancer.
- Taxol acts as a chemotherapeutic agent by binding to tubulin in microtubules, which prevents spindle formation during cell division. This prevents growth of the tumour.
- Taxol is a chiral molecule with 11 chiral carbon centres. Many diastereoisomers are therefore possible.
- Taxol is now produced in semi-synthetic synthesis starting with extracts from yew needles. The reactions involve the use of a chiral auxiliary. This binds to the reactant in such a way that it determines the stereochemistry of the next step.
- Enantiomer selectivity is common in the drug industry as different enantiomers often have different effects in the body.
- A polarimeter can be used to identify enantiomers.

D.8 Nuclear medicine

Nuclear radiation, whilst dangerous owing to its ability to damage cells and cause mutations, can also be used to both diagnose and cure diseases.

- Medical treatment uses radioisotopes that are alpha, beta, gamma, proton, neutron, or positron emitters.
- Radioactive emissions have ionizing effects in cells.
- The half-life of a radioactive isotope is the time taken for an initial amount of substance to fall to one half of its initial value. Radioactive decay reactions have a constant half-life; they are first-order reactions. The shorter the half-life the greater the activity of the radionuclide.
- Diagnostic approaches use MRI, an application of NMR, and PET scanners.
- The tracers used in diagnosis include technetium-99m, which is a gamma emitter. It has a convenient half-life (6 hours), and binds well to a range of biologically active substances.
- Radionuclide therapy can be internal or external. External therapy generally uses cobalt-60.
- Internal radionuclide therapy includes target alpha therapy using lead-212, and boron neutron capture therapy.
- Side-effects of radiotherapy include nausea, sterility, skin damage, and fatigue.

D.9 Drug detection and analysis

A variety of analytical techniques is used for detection, identification, isolation, and analysis of medicines and drugs.

- Drug preparation usually involves techniques of separation and purification, exploiting differences in solubility and volatility.
- Solvent extraction separates components of a mixture on the basis of their partition between different solvents.
- Recrystallization involves crystallizing a product out from a hot solvent, in which impurities are more soluble.
- Fractional distillation separates mixtures into fractions on the basis of their different boiling points. The vapour above a mixture of liquids is always enriched in the more volatile component. Successive cycles of boiling and condensation cause greater separation of the components.
- Raoult's law states that the vapour pressure of a volatile substance in a solution is equal to the vapour pressure of the pure substance multiplied by its mole fraction.
- Drug detection relies on accurate analytical instrumentation.
  - Steroid detection uses gas chromatography and mass spectrometry.
  - Alcohol detection uses breathalysers based on redox reactions or fuel cells.
- Characterization of drugs uses mass spectrometry, IR spectroscopy, and NMR spectroscopy.

D.6 Environmental impact of some medications

The synthesis, isolation, and administration of medications can have an effect on the environment.

- Solvent waste is a major emission of the pharmaceutical industry. Environmental issues include by-products of incineration and the direct consequences on soil and water of dumping toxic compounds.

- Medical nuclear waste includes low-level waste and high-level waste. Some radioisotopes from medical diagnosis generate high-level waste, and secure means are needed to preventing this from entering the soil and water supply.
- Antibiotic resistance is an increasing problem that demands global measures for the controlled use of antibiotics.
- The antiviral drug tamiflu can be prepared using Green Chemistry principles, including the isolation of the precursor from fermentation reactions.
- Green Chemistry principles are helping to reduce waste and reduce the environmental impact of many aspects of the pharmaceutical industry.