Option D Medicinal Chemistry

D1. Pharmaceutical products and drug action

Understandings:

In animal studies, the therapeutic index is the lethal dose of a drug for 50% of the population (LD_{50}) divided by the minimum effective dose for 50% of the population (ED_{50}).

In humans, the therapeutic index is the toxic dose of a drug for 50% of the population (TD_{50}) divided by the minimum effective dose for 50% of the population (ED_{50}).

The therapeutic window is the range of dosages between the minimum amounts of the drug that produce the desired effect and a medically unacceptable adverse effect.

Dosage, tolerance, addiction and side effects are considerations of drug administration.

Bioavailability is the fraction of the administered dosage that reaches the target part of the human body.

The main steps in the development of synthetic drugs include identifying the need and structure, synthesis, yield and extraction.

Drug–receptor interactions are based on the structure of the drug and the site of activity.

Applications and Skills:

Discussion of experimental foundations for therapeutic index and therapeutic window through both animal and human studies.

Discussion of drug administration methods.

Comparison of how functional groups, polarity and medicinal administration can affect bioavailability.

Guidance:

For ethical and economic reasons, animal and human tests of drugs (for LD50/ED50 and TD50/ED50) respectively should be kept to a minimum.

Drugs

The effects of drugs and medicines

A drug is a natural, synthetic or semi-synthetic substance that results in one or more of the following changes within the body:

Alters incoming sensory sensations (from eyes, ears and other sense organs).

Alters mood or emotions.

Alters the physiological state, including consciousness, metabolic activity level or coordination.

Medicinal drugs (medicines or pharmaceuticals) are taken to improve the physical and mental health. They have a therapeutic action that benefits the body.

OTC refers to Over-The-Counter, drugs that can be bought at a pharmacy and not requiring a prescription from a medical doctor. Examples include mild analgesics (pain killers) and antacids.

Administration of drugs

The majority of drugs need to be absorbed into the blood stream to reach their target cells. The method of drug administration determines the biological route taken by the drug and the rate at which it enters the plasma of the blood.
The five main methods of drug delivery are: **oral (by mouth), inhalation (into the lungs), rectal (through the blood vessels of the anus) and by injection (parenteral)** using a hypodermic needle, a faster absorption method for the drug to enter the bloodstream. Some drugs in the form of creams can also be applied topically onto the skin (transdermal).

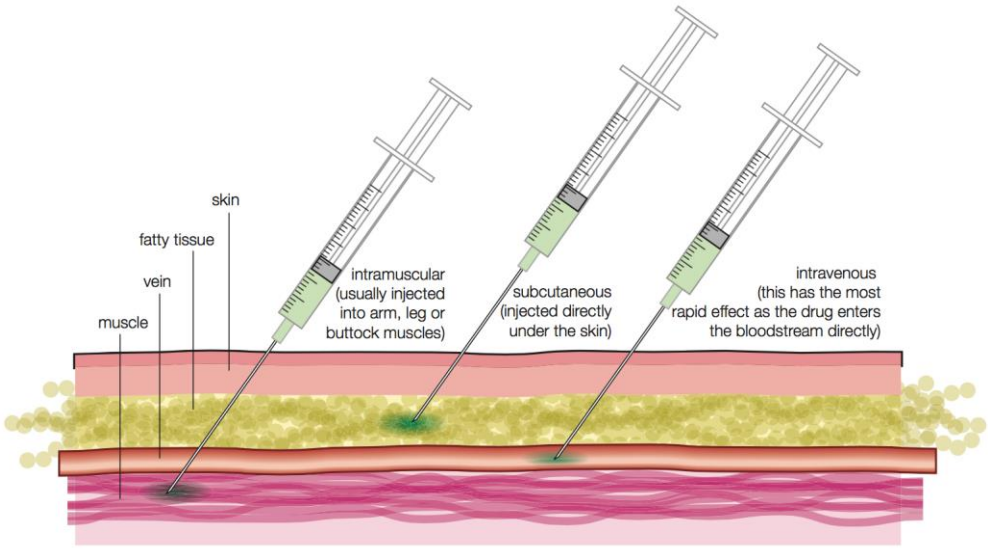


Figure 1.1

Summary of common methods of drug delivery by injection

Development and testing of new medicinal drugs

The research and development of new drugs is a long and expensive process. A new **lead compound** (with biological activity) may be isolated and purified from an existing species, often a plant, fungus or marine organism. However, medicinal drug development often starts by finding an active compound from 'chemical libraries' containing thousands of synthetic drugs.

A lead compound is often chemically modified to improve its physical properties and biological effects. Some new medicinal drugs are developed by a process of rational design. They are designed and synthesized knowing the structure and shape of the receptor the drug molecule interacts with.

A potential drug candidate needs to undergo extensive testing *in vitro* testing with bacteria, cells or biological molecules and later with animals. Anti-cancer drugs, are tested with cancer cells grown in culture. The results of large scale animal testing will establish the lethal dose required to kill 50% of the animal test population. This is known as the LD_{50} value, but it is also important to carry out tests that identify chronic, long term toxicity, which is non-lethal.

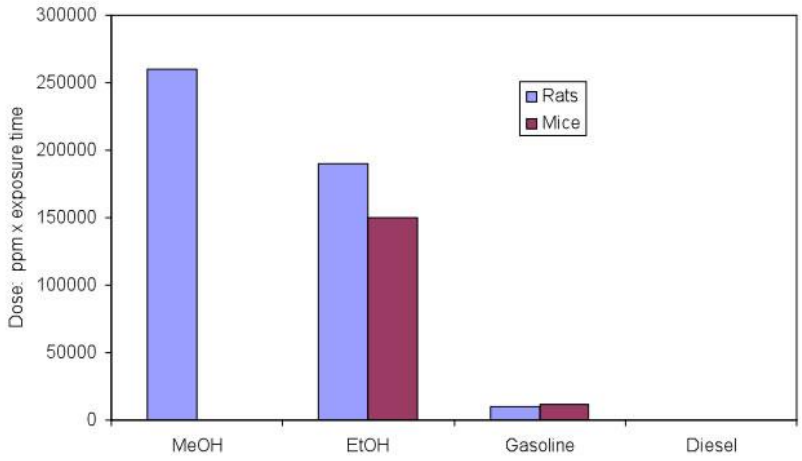


Figure 1.2 Inhalation LD_{50} values of common fuels

A large LD_{50} value means that the substance is relatively non-toxic and that a large quantity of the substance is required to cause a toxic response. A small LD_{50} value means that the substance is relatively toxic and that only a small quantity of the substance is needed to cause a toxic response.

The effective dose required to bring about a measureable effect in 50% of the test animal population will also be determined. This is known as the ED_{50} value. The therapeutic index for animals = $\frac{LD_{50}}{ED_{50}}$.

Drugs will then be subjected to a variety of clinical testing phases with volunteers (first phase) and at later stages with human patients subject to approval by a drug regulatory authority, for example, FDA (Food and Drug Administration) in US. In humans the **therapeutic index** = $\frac{TD_{50}}{ED_{50}}$, where TD_{50} represent the toxic dose for 50% of the human test population.

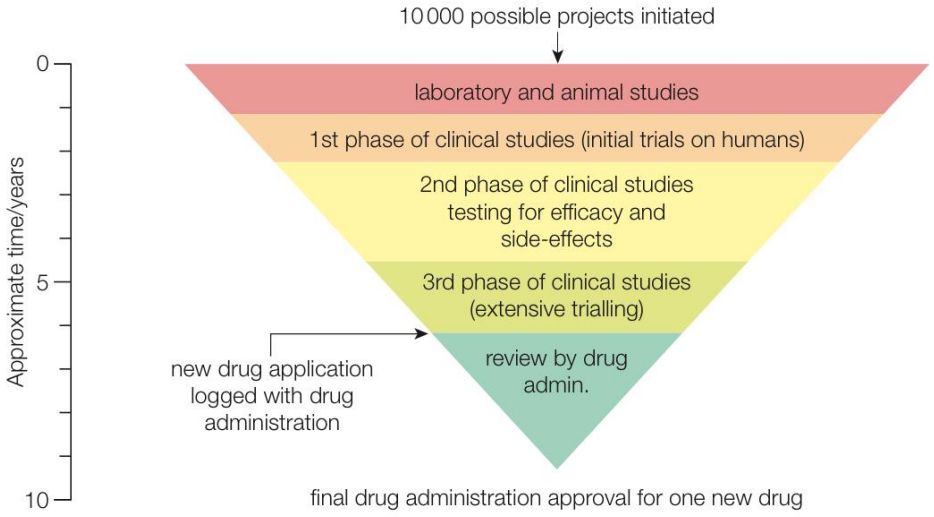


Figure 1.3 Summary of the steps in the development of a new drug

Human clinical trials will indicate whether there are any short term side effects and allow the therapeutic window to be established. **Therapeutic window** is the range of dosage between the <u>minimum</u> dose required to produce a therapeutic effect and the level which produces unaccepted toxic effects.

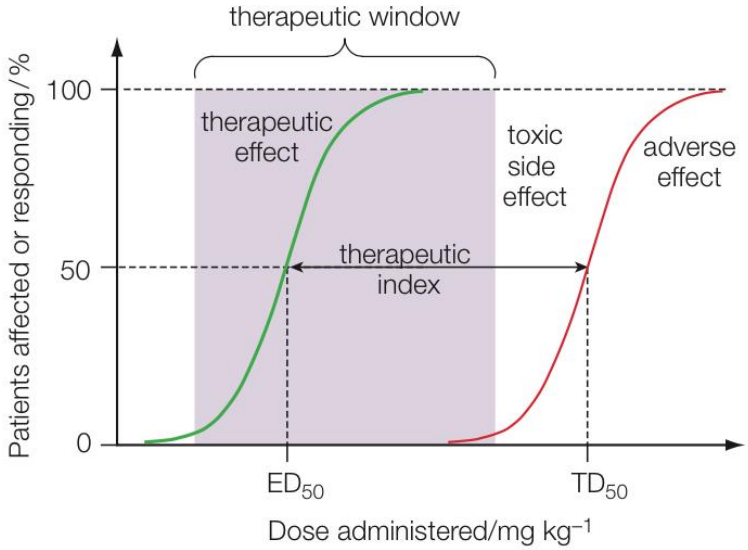


Figure 1.4 The therapeutic index and therapeutic window

All substances are potentially poisonous: it is only the dose that determines whether a substance is poisonous. The concepts of toxicology imply that no drug is 100% safe.

Side effects of a drug are unwanted, unintended and sometimes harmful effects that appear with a dose within the therapeutic window. A risk to benefit ratio will determine whether the drug's side effects are critical. For example, side effects may be considered less of an issue if the drug is shown to be highly effective at treating a particular condition or infectious disease. They usually increase with dosage.

During drug testing on human patients, half of the clinical patients are administered with the drug and the other half are given an inert chemical **placebo**, which resembles the drug in appearance and taste, but has no bioactive chemicals.

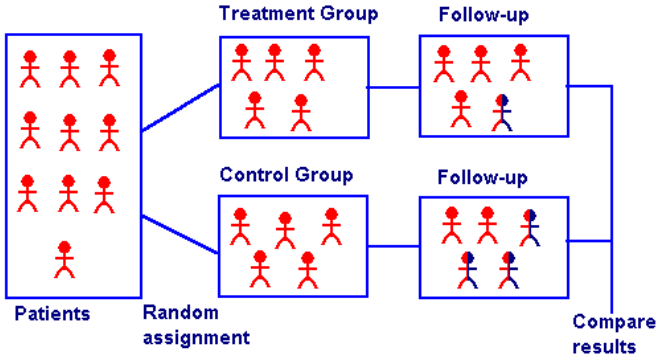


Figure 1.5 Drug testing

The placebo effect occurs when a placebo promotes the 'natural healing' effects of the human body. Any medicinal drug needs to be more effective than a placebo during the trial phase of drug lead testing. It is not clear why the placebo works, but a person's hope about a treatment can trigger a biochemical effect presumably via the immune system and endocrine (hormone) system.

Figure 1.6 A test drug and placebo identical in appearance, taste and texture

Tolerance and addiction

Tolerance towards a drug often occurs as the body's immune system and target cells adapts to the continued presence of a drug. A person who develops tolerance will require **larger doses of the drug** to achieve the same biological effect. Tolerance raises the risk of dependence and reaching a toxic or lethal dose. Some drugs, especially opiates (see section D.3) can

also cause addiction, where the body is likely to experience withdrawal symptoms occur when the drug is not taken or the dose decreased.

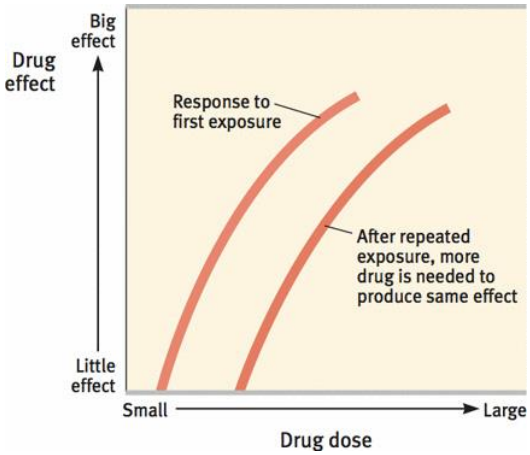


Figure 1.7 Tolerance

Drug action

Drugs bring about their effects by reversibly binding to receptors. These receptors are usually proteins located within the cell membrane, cytoplasm or cell nucleus. The drug molecule and receptor (often an enzyme) have an induced fit relationship. Their interaction is reversible and involves the formation of a variety of weak intermolecular interactions.

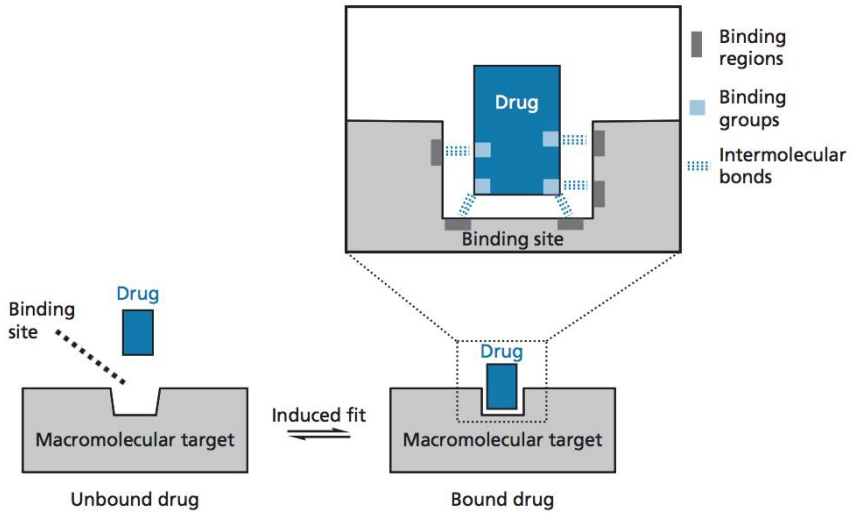


Figure 1.8 The equilibrium of a drug being bound and unbound to its target molecule

Drugs can have different biochemical effects on their target receptor (protein).

Extension materials

Agonistic: the drug molecule acts in a very similar way to the normal substrate, activating the receptor upon binding and producing a similar biological response

Antagonistic: the drug molecule blocks the substrate-binding site and stops the natural substrate from binding and activating the receptor.

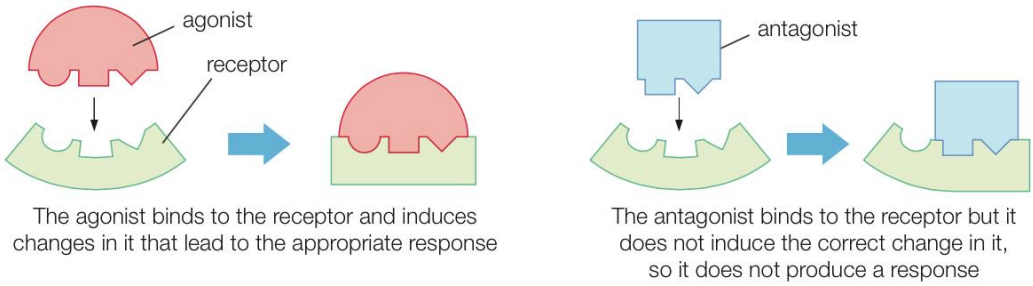


Figure 1.9 An illustration of an agonist and an antagonist binding to a receptor site on a protein molecule

Allosteric: the drug molecule binds to a site on the surface of the protein other than the substrate-binding site. This action changes the three-dimensional shape of the protein which may increase or decrease the receptor's response to the natural ligand.

An ionic or electrostatic bond is the strongest of the intermolecular bonds (20–40 kJ mol^{-1}) and takes place between groups that have opposite charges, such as a carboxylate ion and an aminium ion ($-NH_3^+$). The strength of the interaction is inversely proportional to the distance between the two charged atoms and it is also dependent on the nature of the environment, being stronger in hydrophobic environments than in polar environments.

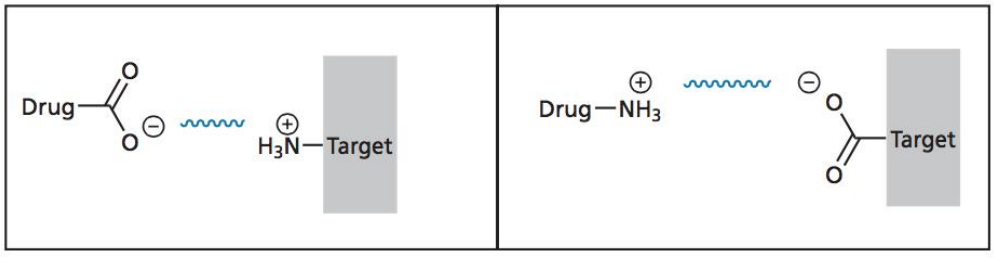


Figure 1.10 Electrostatic (ionic) interactions between a drug and the binding site.

Extension materials

The role of water and hydrophobic interactions

An important feature of the interaction of a drug with its target is the role of water. The macromolecular targets (usually cell membrane proteins) in the body exist in an aqueous environment and the drug has to travel through that environment, so both the drug and macromolecule target are hydrated with water molecules before they meet each other.

The water molecules surrounding the drug and the target binding site have to be stripped away before the interactions described below can occur. The diagram shows an ester (drug) interacting with the hydroxyl side chain in the binding site of the target.

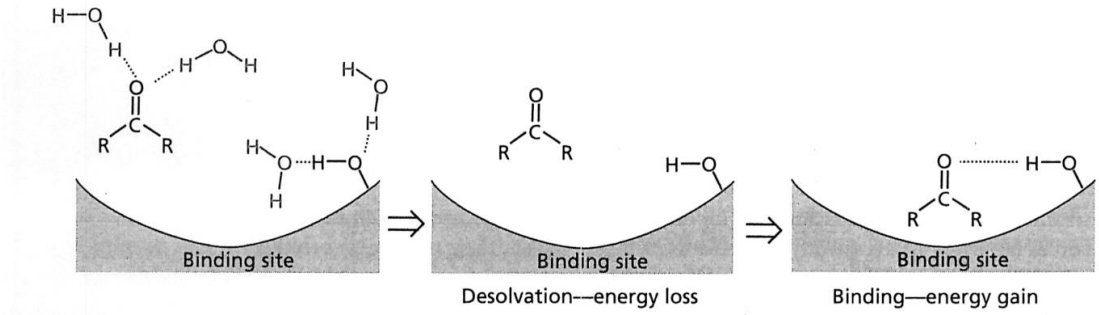


Figure 1.11 De-solvation of a drug and its target binding site before binding

This requires energy, and if the energy required to de-solvate both the drug and the binding site is greater than the energy gained by the binding interactions, then the drug may be ineffective.

It is not possible for water to hydrate the non-polar or hydrophobic regions of a drug or its target binding site. Instead, the surrounding water molecules form stronger than usual interactions with each other, resulting in a more ordered layer of water next to the non-polar surface. This represents a negative entropy change due to the decrease in randomness and distribution of energy.

When the hydrophobic region of a drug interacts with a hydrophobic interaction of a binding site, these water molecules are released and become less ordered. This leads to an increase in entropy and a gain in binding energy.

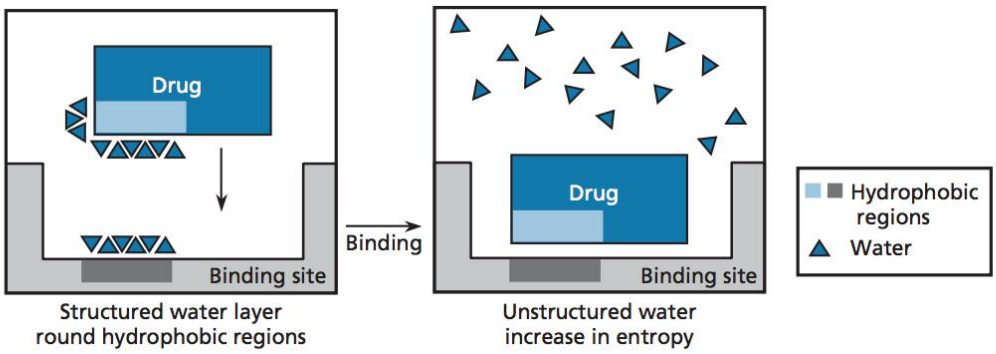


Figure 1.12 Hydrophobic interactions

Bioavailability

The **bioavailability** of a drug is the fraction of the administered dosage that reaches the target part of the human body for activity in the target tissue cells. Bioavailability is affected by dissolution of solids (drugs may be molecular or ionic), absorption into the blood (if not administered intravenously), distribution to tissues, by the circulatory system, metabolism to inactive compounds and excretion mostly through urine via the kidneys.

Bioavailability affects the effectiveness (or efficacy) of the drug and determines how much drug has to be administered. A drug that is difficult to dissolve in water will be absorbed slowly. Time release capsules have various coatings to ensure gradual release of the drug over time. The form a drug is available in, as a tablet or in liquid form, and whether it is taken on an empty stomach or with food determines the rate at which the drug is absorbed.

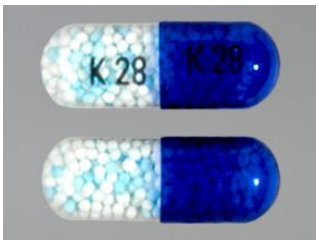


Figure 1.13 Phentermine hydrochloride (time release capsules)

Except for intravenous injections, a drug must be transported across the blood vessels, which contain a fatty or lipid layer (the cell membrane). Drugs which dissolve readily in fats (lipophilic) are therefore more easily absorbed. Drugs can be absorbed into the blood stream from a region of high to low drug concentration, by simple diffusion.

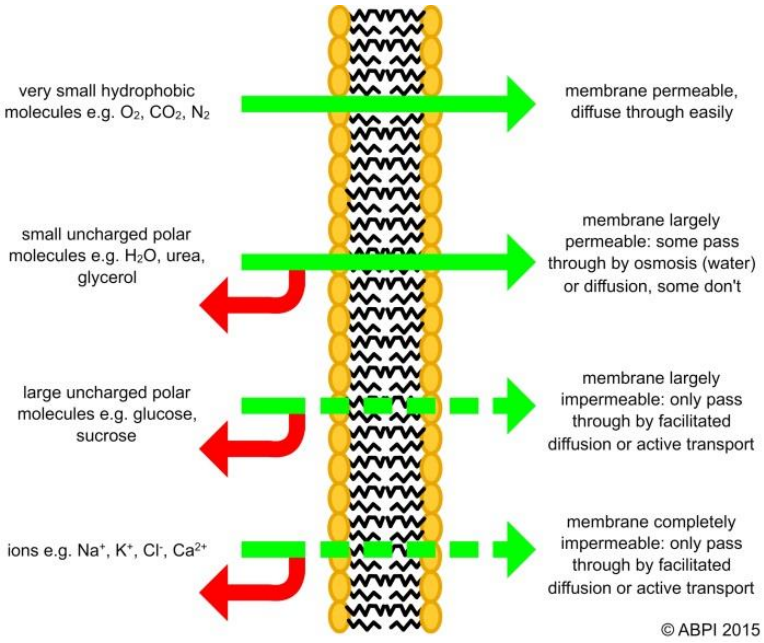


Figure 1.14 Structure of a cell membrane and membrane transport mechanisms

The capillaries of the brain are denser and prevent diffusion of many substances into the neurons of the brain, this structure is termed the blood-brain barrier). For example, penicillins do not past this barrier. This is fortunate since they cause convulsion if injected directly into the brain. Psychoactive drugs, such as LSD (‘acid’), can pass into the brain as these drugs alter behavior or change consciousness, by binding to various protein receptors on the surface of brain cells in the brain.

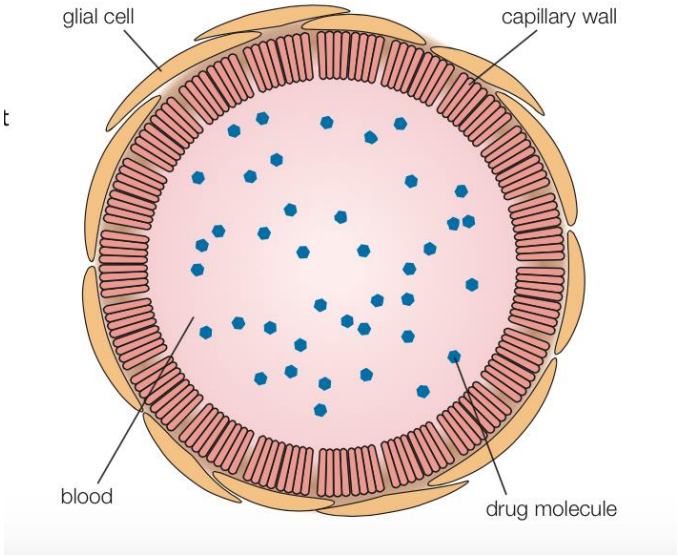


Figure 1.15 Blood brain barrier

Effect of function group on bioavailability

The interaction between the drug and the receptor is due its complementary nature, analogous to the ‘lock and key’ action of enzymes with substrate. The functional groups within the drug structure interact with the receptors of a biological target at the site of activity which is normally composed of amino acids in the form of a protein or glycoprotein (protein with sugars). Functional groups can determine solubility as well as electronic and steric influences which affect the bioavailability. These include:

Hydrophilic functional groups increase water solubility and lipophilic functional groups increase lipid solubility both affect drug absorption into the blood.

Functional groups that dissolve in acidic environments will be absorbed through the stomach lining whereas in alkaline conditions in the small intestine (located after the stomach) will absorb different functional group. In either case, the drug passes through the liver and is metabolized (by various enzymes) before reaching the blood stream, decreasing bioavailability.

Effects of bioavailability on the route of administration

The bioavailability of morphine is found to be about 20-40% taken orally, 35-70% inserted rectally, and 100% via intravenous injection. Bioavailability depends on the method of administration, how the drug is absorbed from the route of administration into the blood, distributed and interacts with receptors.

For example, a drug can be injected intravenously and enters directly into the blood stream as it experiences no barriers to absorption. It is therefore ideal for delivery of an accurate dose in emergency cases where rapid absorption the drug is required.

Drugs administered via breathing (inhalation) tend to be lipid soluble, small molecules that enter the respiratory tract lining rapidly due to the extensive network of blood vessels in the lungs and can be as effective as the intravenous method.

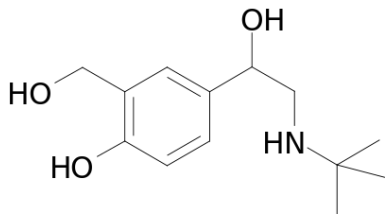


Figure 1.16 Salbutamol (ventolin) – used to treat asthma via inhalation

If a drug is taken orally, it must be water soluble and thus dissolve in the stomach. Some may be inactivated by the acid, be absorbed across the stomach and/or the intestinal wall if it has some alkaline condition before being circulated through the blood. The bioavailability of an oral medication

depends on drug solubility and pH. It also depends on whether it is taken on an empty stomach or a full stomach and the effects of other drugs.

The first-pass effect is a phenomenon of drug metabolism whereby the concentration of a drug is greatly reduced before it reaches the systemic circulation (blood except that and from the lungs). It is the fraction of drug lost during the process of absorption which is generally related to the liver and gut wall. Notable drugs that experience a significant first-pass effect are morphine, diazepam (an anti-depressant) and lidocaine.

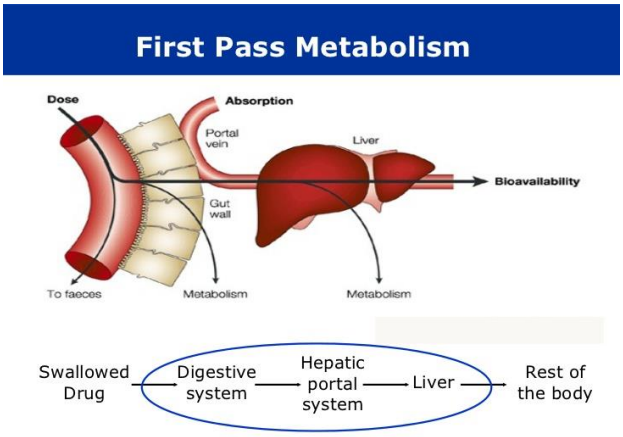


Figure 1.18 The First Pass Effect

Serendipity in drug discovery

During World War II, a US ship carrying mustard gas exploded in an Italian harbour. It was observed that many of the survivors who had inhaled the gas lost their natural defences against microbes. Further study showed that their white blood cells had been destroyed. It is perhaps hard to see how a drug that weakens the immune system could be useful. However, there is one disease where this is the case—leukemia. Leukemia is a form of cancer which results in the excess proliferation of white blood cells, so a drug that kills these cells is potentially useful. As a result, a series of mustard-like anti-cancer drugs were developed based on the structure of the original mustard gas, which work by inhibiting DNA replication.

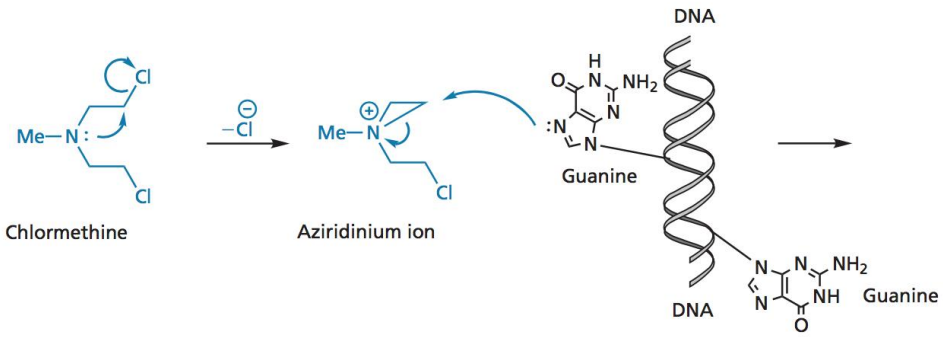
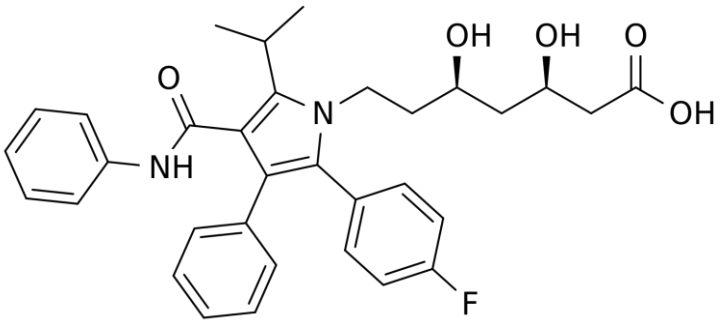


Figure 1.19 Initial step in the action in the alkylation of DNA by chlormethine

Activity D1

The structure of Atorvastatin (shown below), and it is marketed under the trade name Lipitor. It is a member of the drug class known as statins, which are used primarily for lowering blood cholesterol and for prevention of events associated with cardiovascular disease.



1. Identify all the functional groups in the molecule.
2. Add asterisks to the two chiral carbon atoms.
3. Do a search for web resources on the Internet and write brief notes on the following to share with the class:
   -Medical uses
   - Administration
   - Possible side effects
   - Contradictions.
   - Mechanism of action
   - Pharmacokinetics
   - Chemical synthesis
   - LD_{50}, ED_{50} and TD_{50}

Photography of Atorvastatin (David Talbot)

D2. Aspirin and penicillin

Essential idea: Natural products with useful medicinal properties can be chemically altered to produce more potent or safer medicines.

Understandings:

Aspirin:

Mild analgesics function by intercepting the pain stimulus at the source, often by interfering with the production of substances that cause pain, swelling or fever.

Aspirin is prepared from salicylic acid.

Aspirin can be used as an anticoagulant, in prevention of the recurrence of heart attacks and strokes and as a prophylactic.

Penicillin:

Penicillins are antibiotics produced by fungi.

A beta-lactam ring is a part of the core structure of penicillins.

Some antibiotics work by preventing cross-linking of the bacterial cell walls.

Modifying the side-chain results in penicillins that are more resistant to the penicillinase enzyme.

Applications and skills:

Aspirin:

- Description of the use of salicylic acid and its derivatives as mild analgesics.
- Explanation of the synthesis of aspirin from salicylic acid, including yield, purity by recrystallization and characterization using IR and melting point.
- Discussion of the synergistic effects of aspirin with alcohol.
- Discussion of how the aspirin can be chemically modified into a salt to increase its aqueous solubility and how this facilitates its bioavailability.

Penicillin:

- Discussion of the effects of chemically modifying the side-chain of penicillins.
- Discussion of the importance of patient compliance and the effects of the over-prescription of penicillin.
- Explanation of the importance of the beta-lactam ring on the action of penicillin.

Guidance:

- Students should be aware of the ability of acidic (carboxylic) and basic (amino) groups to form ionic salts, for example soluble aspirin.

Structures of aspirin and penicillin are available in the data booklet in section 37.

Aspirin

Aspirin is a mild analgesic (pain killer) and can be prepared in the laboratory by reacting 2-hydroxybenzoic acid (salicylic acid) with ethanoic anhydride (in the presence of concentrated sulfuric acid, which acts as a catalyst). Aspirin (2-ethanoyl-2-hydroxybenzoic acid)) is the ethanoate ester of 2-hydroxybenzoic acid. Ethanoyl chloride (acetyl chloride) can also be used.

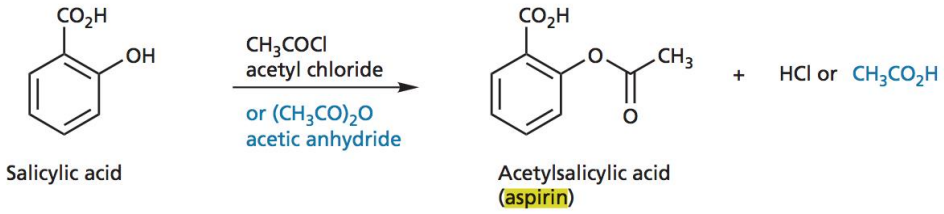


Figure 2.1 Reaction between salicylic acid and ethanoic anhydride to form aspirin

The crude (impure aspirin) crystals can be removed by suction filtration, washed with cold water and then purified by recrystallization. The product can be recrystallized from hot solvent such as ethanol to obtain pure aspirin. Soluble impurities, e.g. the unreacted salicylic acid, are left in solution.

The experimental yield can be measured from the mass of pure aspirin obtained and the percentage yield can be calculated using the stoichiometric equation and molar masses of reactant and products.

The purity of the aspirin can be determined from the melting point of the crystals. The presence of impurities will lower the melting point and cause it to melt over a wider range of temperatures.

Characterisation of aspirin

Determination of the purity of aspirin

How pure a sample of aspirin is can be determined by chromatography or by measuring its melting point. A pure substance will melt at a well defined temperature but the presence of impurities lowers the melting point and causes the solid to melt over a range of temperatures. The melting point of aspirin is reported as 138 –140 °C so if a sample of aspirin is tested and its melting range is found to be 125 –132 °C it can be concluded that the sample is quite impure.

Infrared spectrum of aspirin

The purity of aspirin can also be investigated by recording the infrared spectrum. It shows two peaks at the carbonyl region: 1680 cm^{-1} and 1750 cm^{-1} due to the presence of two carbonyl (C=O) groups, namely an ester and a carboxyl group. There is a very broad absorption peak at 2500 − 3500 cm^{-1} due to the O−H bond in the carboxylic acid group, -COOH.

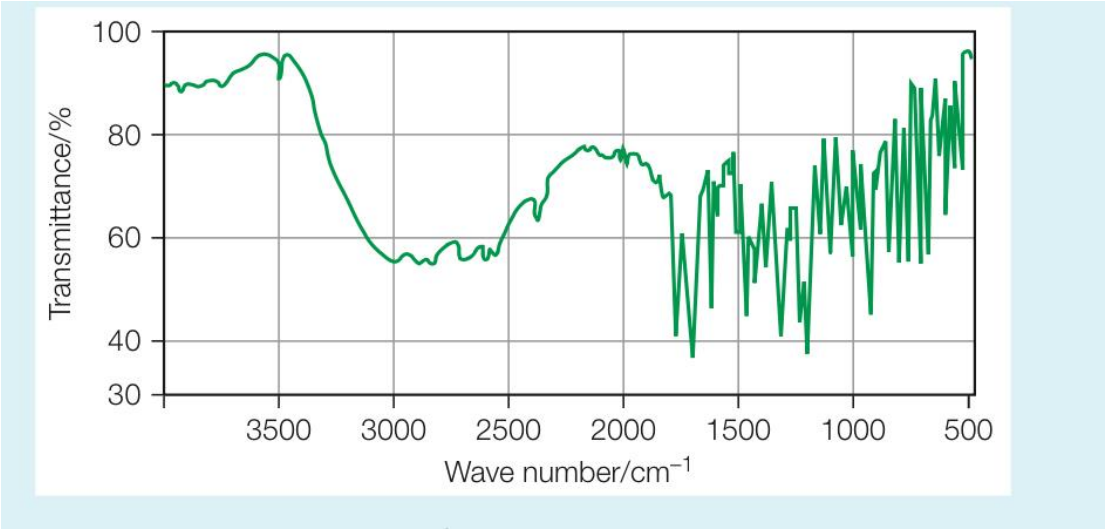


Figure 2.2 The infrared spectrum of aspirin

Therapeutic properties of aspirin

Aspirin can be used as an antipyretic (to reduce fever), an anti-inflammatory and an anticoagulant (to make the blood thinner and be more easily pumped), in prevention of the recurrence of heart attacks and strokes and as a prophylactic.
Salicylic acid (2-hydoxybenzoic acid) is also an analgesic but irritates and damages the mouth, oesophagus and stomach lining. It can be extracted from the bark of a willow tree but was replaced by aspirin.

Mode of action

The mechanism of aspirin's analgesic properties involves inhibiting the enzyme cyclooxygenase at the site of an injury. The enzyme is involved in catalyzing the formation of substances known as prostaglandins. They accumulate at the site of injury and are involved in the transmission of nerve impulses to the brain (which are interpreted as pain).
The most common side effect of aspirin is that it can cause bleeding in the lining of the stomach. This effect is increased when taking aspirin tablets with alcohol (ethanol) which has a synergistic effect.

Young children are not advised to take large dosages of aspirin during a viral infection since it is linked to Reye's syndrome, a potentially fatal liver and brain disorder. Aspirin causes convulsions if injected into the brain. This is a toxic effect caused by the release of 2-hydroxybenzoic acid by hydrolysis. Very large

dosages of aspirin orally can be fatal due to acidosis, a lowering of the pH of the blood.

Soluble salt of aspirin

The molecular or free acid form of aspirin has limited solubility in water (due to the presence of the non-polar benzene ring). It is in equilibrium with its carboxylate anion and its bioavailability in blood is limited.

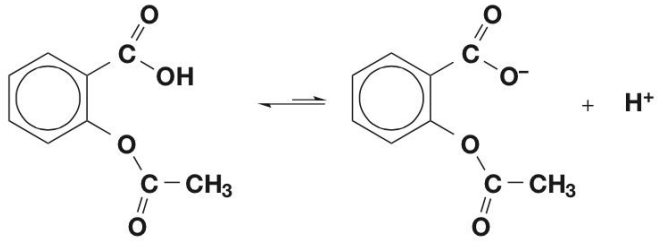


Figure 2.3 Partial dissociation of aspirin in water

The carboxylic acid group of aspirin can be ionized via a neutralization reaction with a strong base to convert to a more soluble ionic form. This is known as ‘soluble aspirin’.

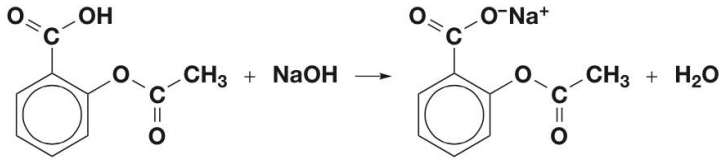


Figure 2.4 Formation of the soluble sodium salt of aspirin

However, once the aspirin anion reaches the acidic gastric juice of the stomach it is converted back to its molecular (free acid) or un-ionized form.

Aspirin is thought of as a ‘safe’ medicine, but like all medicines it is only safe if taken in the recommended dose. The lethal dose is 30 g for an adult of average size. A typical tablet contains 0.3 g, so 100 aspirin tablets could be a lethal dose. Unpleasant symptoms would be experienced with far fewer tablets than this. The recommended dose of aspirin is no more than 12 tablets a day, and it is not recommended for children under 12 years old.

Extension materials

Paracetamol

Paracetamol (UK) or acetaminophen (US), like aspirin, relieves pain and reduces fever, but unlike aspirin does not reduce stiffness, redness and the swelling symptoms of arthritis. It has very few side-effects when taken as directed for a short period, but should not be taken with alcohol, nor by patients with kidney or liver disease. It is the preferred treatment for patients with aspirin allergy, ulcers or clotting disorders. However, there is some evidence that people who take high doses of it and drink large amounts of alcohol will have an increased risk of liver damage. The differences between aspirin and paracetamol are summarized in the table below.

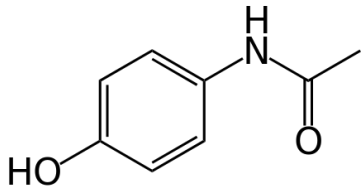


Figure 2.5 Structure of paracetamol

	Aspirin	**Paracetamol**
Causes gastrointestinal tract blood loss?	Yes	No
Increases the tendency to bleed?	Yes	No
Thins the blood and prevents clots from forming?	Yes (effective against heart attacks and strokes)	No
Can cause an allergic reaction?	Yes	No, because it is not a salicylate
Potential for causing nausea and vomiting?	More	Less
Possesses anti-inflammatory action?	Yes and hence used in treating rheumatoid arthritis	Weakly anti-inflammatory
Potential to act as a suicide drug?	Yes	Yes
Anti-pyretic	Yes	Yes

Antibacterials

General structure

Penicillins are a group of antibiotics originally isolated from a mould named *penicillium notatum*. Antibiotics are substances that kill bacteria or inhibit the growth of bacteria.

Penicillins are known as beta-lactam antibiotics and their general structure is shown below in Figure 2.6. The penicillins differ in the chemical nature of the acyl side chain. All penicillins contain a reactive functional group known as the **beta lactam** ring which is a strained four membered cyclic carboxamide with bond angles of 90 degrees. The ring is under strain (high energy) which makes the carboxamide group within the ring system highly reactive and opens up easily.

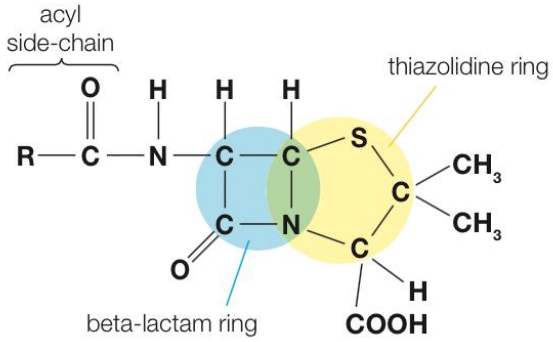


Figure 2.6 Generalized structure of the penicillins

A **broad-spectrum antibiotic** is active against a wide range of bacterial diseases or bacterial strains. A **narrow-spectrum antibiotic** is active against only a small range of bacterial diseases or bacterial strains.

Extension materials

Bacteria are single celled microorganisms, many are harmless or beneficial but some cause infectious diseases. Their cell membrane is surrounded by a protective cell wall that is formed from covalently linked amino acids and sugars.

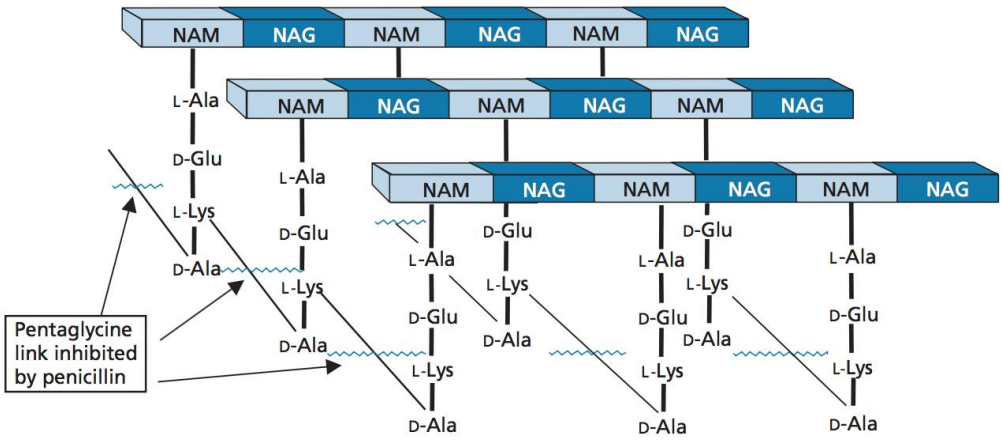


Figure 2.7 Simplified structure of the bacterial cell wall

Penicillin acts by irreversibly inhibiting the bacterial enzyme (transpeptidase)involved in catalysing the formation of cross links that give the bacterial cell wall its strength. The absence of cross links makes the bacterial cell permeable to water which enters via osmosis. The build-up of osmotic pressure causes the bacterial cell to swell and bursts (lyses).

Extension materials

The final step involves the enzyme-controlled cross-linking and penicillin resembles the dipeptide (alanine–alanine) that is part of the substrate by the transpeptidase enzyme for the cross-linking reaction.

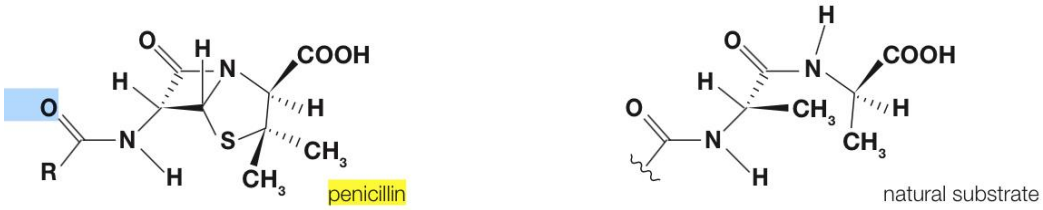


Figure 2.8 Structures of penicillin and alanine–alanine:the substrate for transpeptidase

The penicillin mimics the shape of the enzyme's normal substrate and hence enters the active site. The enzyme becomes covalently attached to the penicillin molecule and is then not capable of catalysing any further reactions.

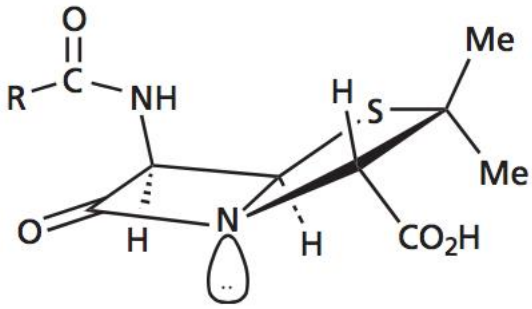


Figure 2.9 Three-dimensional structure of penicillin

Antibiotic resistance

Some bacteria in a population of a strain of bacteria may be naturally resistant to the effect of an antibiotic. For example, some strains of bacteria secrete an enzyme known as penicillinase which hydrolyses penicillin G (where R is the benzyl group, $--CH_2-C_6H_5$). Penicillin G was the first penicillin to be developed but had to be injected intravenously because it was hydrolyzed by the acid in the stomach.

Medicinal chemists have synthesized a large number of other penicillins which have a chemically modified side chain, for example, penicillin V where R = $C_6H_5OCH_2-$). This molecule has a different structure and shape from penicillin G and does not act as a substrate for pencillinase. It is resistant to hydrolysis by gastric juices.

Patients not completing the full prescribed course of antibiotics and the use of antibiotics in animal feeds has contributed to the development of antibiotic resistance. This means that the bacterium is resistant to one more antibiotics. The antibiotics can also enter human via eating meat and milk products (though there are regulations to prevent this from happening). Ove-prescription of antibiotics can also lead to the development of antibiotic resistance.

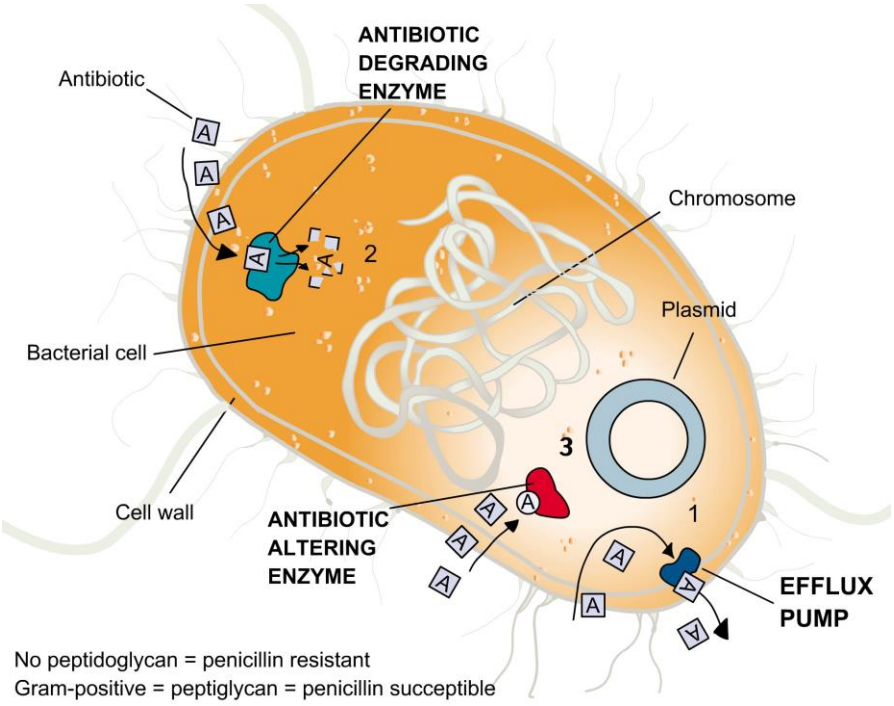


Figure 2.10 Action of antibiotics

Bacteria either have pre-existing resistance to drugs, or they develop resistance. Often resistance to a certain drug from a particular class leads to resistance to all other drugs in that class.

D3. Opiates

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

Understandings:

The ability of a drug to cross the blood–brain barrier depends on its chemical structure and solubility in water and lipids.

Opiates are natural narcotic analgesics that are derived from the opium poppy.

Morphine and codeine are used as strong analgesics. Strong analgesics work by temporarily bonding to receptor sites in the brain, preventing the transmission of pain impulses without depressing the central nervous system.

Medical use and addictive properties of opiate compounds are related to the presence of opioid receptors in the brain.

Applications and skills:

Explanation of the synthesis of codeine and diamorphine from morphine.

Description and explanation of the use of strong analgesics.

Comparison of the structures of morphine, codeine and diamorphine (heroin).

Discussion of the advantages and disadvantages of using morphine and its derivatives as strong analgesics.

Discussion of side effects and addiction to opiate compounds.

Explanation of the increased potency of diamorphine compared to morphine-based on their chemical structure and solubility.

Guidance

Structures of morphine, codeine and diamorphine can be found in the data booklet in section 37.

Opiates

Opiates are **natural narcotic analgesics** that are derived from the opium poppy (*Papaver somniferum).* The unripe seed pods contain opium and are the source of morphine and codeine. Opiates are natural alkaloids found in opium. Alkaloids are nitrogen-containing bases extracted from plants.

Figure 3.1 Opium poppy (with latex)

Morphine is a powerful painkiller (strong analgesic) with sleep-inducing properties (narcotic). Morphine is only available on prescription and is given to relieve the pain caused by severe injury, surgery and pain caused by cancer. Codeine is used in cough mixtures and is a less powerful analgesic.

Diamorphine is a semi-synthetic morphine derivative. The difference between the structures is that diamorphine contains two ester (CH_3COO) groups, whereas morphine contains two - OH groups. Morphine can also be converted to codeine, by replacing a hydroxyl group, -OH on the benzene ring to methoxyl group (ether group), $-OCH_3$.

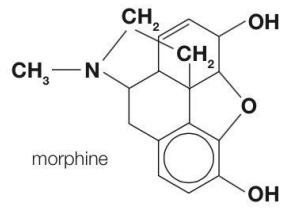


Figure 25.67 Structure of morphine

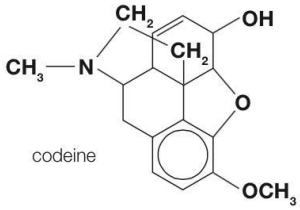


Figure 25.68 Structure of codeine

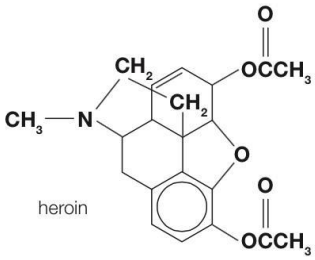


Figure 25.69 Structure of heroin

Figure 3.2 Structure of morphine, codeine and diamorphine(heroin)

They work as analgesics by binding and interacting with opioid protein receptors on the surfaces of brain cells (neurons). They prevent nerve impulses (pain signals) from causing changes inside brain cells without depressing the central nervous system (brain and spinal cord).

Extension materials

Morphine is a *chiral* molecule containing several asymmetric centres and exists naturally as a single stereoisomer. When morphine was first synthesized, it was made as a racemic mixture of the naturally occurring enantiomer with its mirror-image enantiomer the activity of synthetic morphine was half that of natural morphine and separation of the enantiomers showed that the unnatural enantiomer had no analgesic activity. This is because the proteins targeted by drugs are themselves asymmetric and are able to distinguish between the enantiomers of a chiral drug.

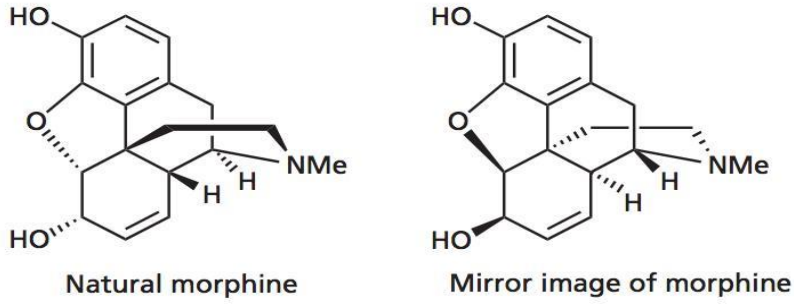


Figure 3.4 Morphine and its mirror image

Diamorphine (heroin)

Diamorphine can be prepared from morphine by reaction with ethanoic anhydride in an esterification reaction (addition-elimination reaction). CH_3COO- is an ester/ethanoate group.

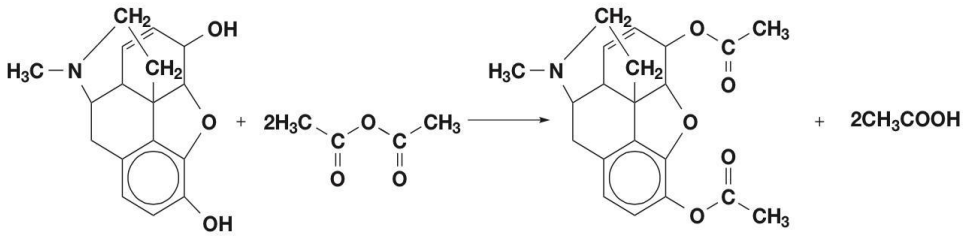


Figure 3.5 The formation of diamorphine (heroin)

Diamorphine is more lipid-soluble (more lipophilic) than morphine because of the replacement of the polar -OH groups by the less polar ester groups and therefore is able to cross the **blood–brain barrier** and enter the brain more easily. The blood–brain barrier is essentially a lipid barrier that prevents the entry of potentially toxic substances from the capillaries into the brain – it allows small, lipid-soluble molecules across and hinders large, polar molecules. Once diamorphine has entered the brain, it is hydrolysed by enzymes to the monoester (only one ester group) and to morphine; these bind to opioid

receptors and produce an analgesic effect. This makes diamorphine about five times more effective as an analgesic than morphine when injected into the blood because it crosses the blood brain barrier in greater quantities.
The morphine and heroin molecules both contain a **tertiary amine** group. They can both be converted into ionic salts by reacting with hydrochloric acid to form a soluble tertiary ammonium salt. Morphine is often injected in the form of morphine hydrochloride to increase its bioavailability. It reverts back to the un-dissociated or free base form to cross the blood-brain barrier.

Codeine

Codeine can be synthesized from morphine. In the original process, morphine was reacted with iodomethane (the methylating agent) in the presence of a base. Phenols are slightly acidic and so the presence of a strong base converts the OH of the phenol to O^-. The reaction is nucleophilic substitution, with the O^- attacking the $\delta+$ carbon atom of the CH_3I.

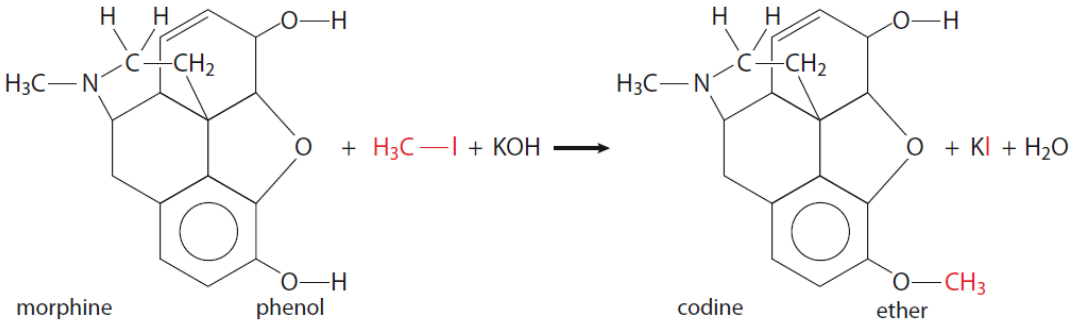


Figure 3.6 Synthesis of codeine from morphine

The synthesis is more usually carried out nowadays using a more complicated methylating agent – a salt of $C_6H_5N(CH_3)$ such as $C_6H_5N(CH_3)^+(C_2H_5O^-)$

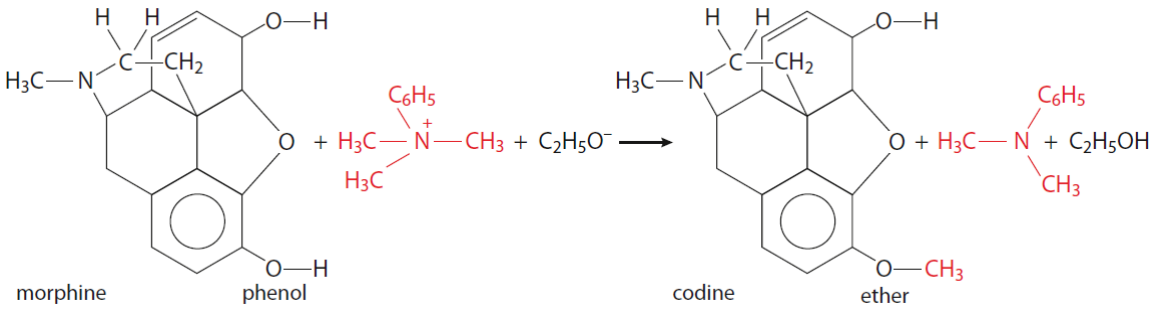


Figure 3.7 A variation on the synthesis of codeine from morphine

Effects of opiates

All of the classical opiates can cause addiction and lead to the development of tolerance and later dependence. Withdrawal symptoms occur within one day for addicts if the drug usage is stopped. These include hot and cold sweats, diarrhoea, anxiety, weakness and muscle cramps that can last for months. The short term and long term effects of strong opiates are summarized below.

Short term effects	Long term effects
Induces a sense of euphoria (great happiness)	Constipation
Relieving of pain (analgesic)	Loss of sex drive
Depress nervous system (sedation); vasodilation (blood vessels widen)	Disrupts the menstrual cycle
Slow breathing rate and heart rate	Reduced appetite
Cough reflex inhibited (antitussive)	Risk of HIV, hepatitis infection etc. through the use of shared needles
High dosages can lead to coma/death via suffocation	Social problems, such as theft and prostitution

Some side effects can be advantageous. For example, the observation that morphine causes constipation has led to the design of opioids which are used in the treatment of diarrhea. Euphoria can be a useful side effect when treating pain in terminally ill patients. However, the effect is not observed in patients suffering severe pain.

Methadone is a **synthetic opioid** frequently used to treat heroin addicts. Although chemically different from morphine and heroin, it acts on the same opioid receptors in the brain and produces many of the same effects with the exception of the euphoria.

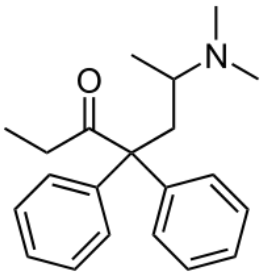


Figure 3.8 Structure of methadone

Methadone's usefulness in treating heroin addicts is due to its long duration of effect and its ability to block the heroin withdrawal symptoms. At high concentrations it can block the euphoric effects of heroin and morphine.

D4. pH regulation of the stomach

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

Understandings

- Non-specific reactions, such as the use of antacids, are those that work to reduce the excess stomach acid.
- Active metabolites are the active forms of a drug after it has been processed by the body.

Applications and skills:

- Explanation of how excess acidity in the stomach can be reduced by the use of different bases.
- Construction and balancing of equations for neutralization reactions and the stoichiometric application of these equations.
- Solving buffer problems using the Henderson–Hasselbalch equation.
- Explanation of how compounds such as ranitidine (Zantac) can be used to inhibit stomach acid production.
- Explanation of how compounds like omeprazole (Prilosec) and esomeprazole (Nexium) can be used to suppress acid secretion in the stomach.

Guidance

- Antacid compounds should include calcium hydroxide, magnesium hydroxide, aluminum hydroxide, sodium carbonate and sodium bicarbonate.
- Structures for ranitidine and esomeprazole can be found in the data booklet in section 37.

Gastric acid in the stomach

The walls of the human stomach contain cells (known as parietal cells) which secrete gastric juices containing hydrochloric acid with potassium chloride, KCl, and sodium chloride, NaCl. The normal pH of gastric juices is in the 1.0-3.0 range.

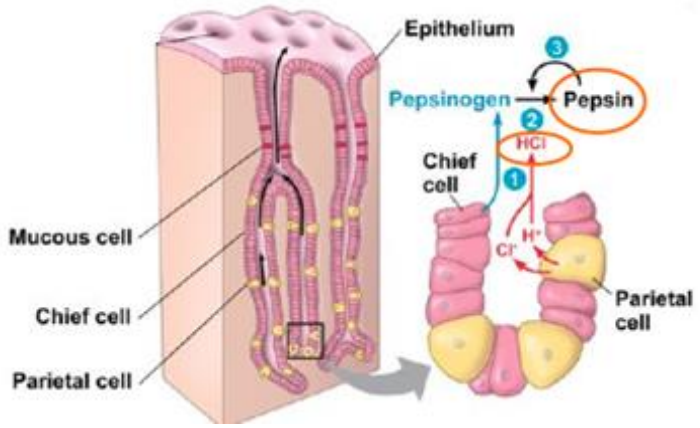


Figure 4.1 Structure of the stomach lining

An acidic environment is essential to the appropriate functioning of the stomach as it:

- Suppresses growth of harmful (pathogenic) bacteria, and
- Helps in digestion by hydrolyzing proteins to amino acids.
- Activates a digestive enzyme, a protease known as pepsin (released as an inactive precursor from Chief cells) which requires a low pH for catalytic activity

Other cells produce hydrogencarbonate ions (HCO_3^-) and gastric mucus to buffer the acid and prevent the gastric juice from digesting the delicate stomach tissues leading to an ulcer. Ulcers are small damaged areas of the mucous membranes of the stomach or small intestine which expose the underlying muscle layers of the gut wall to hydrochloric acid and pepsin.

For many years the ultimate cause of stomach ulcers was not known but evidence accumulated that ulcers (and stomach cancer) are caused by a bacterium, *Helicobacter pylori* which is found under the layers of mucus in the stomach lining, where the pH is only 4 compared to the value of 1 for the gastric juice. The bacterium produces massive quantities of an enzyme called urease which hydrolyses urea and leads to the production of ammonia. This protects the *H. pylori* bacteria from the surrounding hydrochloric acid.

Antacids

Dyspepsia is a clinical symptom that could be due to indigestion, peptic ulcers or gastric or esophageal cancer. Indigestion, occurs when excess gastric juice (hydrochloric acid) is secreted by the stomach and there is reflux into the esophagus. The acid reflux is termed ‘heart burn’.

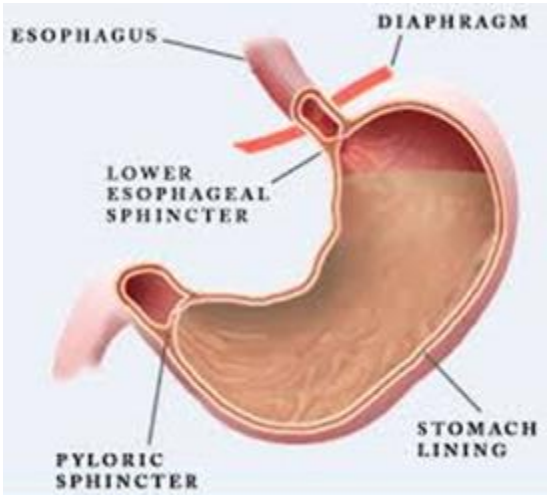


Figure 4.2 The structure of the stomach

Antacids are medicines that reduce excess hydrochloric acid in the stomach. Unlike other drugs they are non-specific and do not bind to cell receptors. They are weak bases and remove the excess hydrogen ions via neutralization. Suitable compounds to act as antacids are metal hydroxides, metal carbonates, metal hydrogen carbonates and some metal oxides. Alkalis are not suitable to be antacids. They are highly corrosive and their neutralization is more exothermic than an insoluble weak base.

Typical neutralization reactions are:

- $NaHCO_3$ (s) + HCl (aq) → NaCl (aq) + H_2O (l) + CO_2 (g)
- $CaCO_3$ (s) + 2HCl (aq) → $CaCl_2$ (aq) + H_2O (l) + CO_2 (g)
- MgO (s) + 2HCl (aq) → $MgCl_2$ (aq) + H_2O (l)
- $Al(OH)_3$ (s) + 3HCl (aq) → $AlCl_3$ (aq) + $3H_2O$ (l)
- $Ca(OH)_2$ (s) + 2HCl (aq) → $CaCl_2$ (aq) + $2H_2O$ (l)

Note that aluminium hydroxide neutralizes three moles of acid (H^+) per mole of base compared to two moles of acid (H^+) neutralized per mole of calcium hydroxide. A calculation based on the mole concept and a balanced equation allows the most effective antacid by mass to be determined.

A comparison of compounds used in antacid preparations

Antacid compound	Action	Side effect
Calcium hydroxide, $Ca(OH)_2$	Although is a strong base, $Ca(OH)_2$ is only slightly soluble in water, and the solution is thus weakly basic. A saturated solution of calcium hydroxide, called limewater, readily neutralizes stomach acid.	An acid buffer exists in the stomach, not in the esophagus; thus the strong base is almost never used as an antacid as extended use can lead to tissue damage.
Magnesium hydroxide, $Mg(OH)_2$	$Mg(OH)_2$ also rapidly neutralized stomach acid but have a laxative effect and can cause diarrhea.	Laxative properties; excess quantities can lead to magnesium toxicity; effect include severe allergic reactions, nausea and black stools (faeces).
Aluminium hydroxide, $Al(OH)_3$	Aluminium hydroxide has a very low solubility in water and dissolves slowly in the stomach to relieve indigestion. It may cause constipation and often is used with magnesium hydroxide, $Mg(OH)_2$, to counteract its side effect to increase bowel movement (urge to pass motion).	The aluminium ion, Al^{3+}, has a high charge density due to its high charge to size ratio and can bind drugs, calcium or phosphate ions thus inhibiting its absorption; depletion of calcium ions, Ca^{2+}, leads to a risk of weaker bones. Its association with Alzheimer's disease is also a concern.
Calcium carbonate, $CaCO_3$	Calcium carbonate, $CaCO_3$, is a strong fast-acting antacid and the same mass works longer than that of sodium hydrogen carbonate, $NaHCO_3$. Also used as a source of calcium (ions) but is not intended for long-term use.	Repeated use as an antacid may lead to excessive amounts of calcium ions being absorbed into the body and may results in kidney stones; calcium carbonate, $CaCO_3$, can produce acid rebound effect by filling up stomach with acid again.
Sodium hydrogencarbonate, $NaHCO_3$ as a solid mixture with citric acid	Reacts in water ("pop fizz") to release carbon dioxide, CO_2 gas; induces belching and flatulence, thus relieving discomfort. $NaHCO_3$ is soluble in water, works quickly and provides short term relief.	The high content fluid retention (bloating) and alkalosis. High Na^+ (aq) concentration leads to high blood pressure, heart failure or kidney problems and may lead to hypertension (high blood pressure).

Activity 4.1

A 10.0 cm^3 sample of gastric juice, obtained several hours after a meal, was titrated with 0.10 mol dm^{-3} NaOH to neutrality; 7.40 cm^3 of NaOH was required. Assume that no buffers were present. Deduce the pH of the gastric juice.

Activity 4.1 Answer:

Amount of NaOH = 0.1 mol dm^{-3} × 7.40 × 10^{-3} dm^3 = 7.40 × 10^{-4} mol =
Amount of H^+ (aq) in 10.0 cm^3 = 7.40 × 10^{-4} mol
$[H^+ (aq)]$ = 7.40 × 10^{-4} mol/ 0.010 dm^3 = 0.074 mol dm^{-3}
pH = - $\log_{10}$ 0.074 = 1.1

Activity 4.2

Many antacids contain alginates and dimethicone. Find out about the nature of these substance and their inclusion in commercial antacids.

pH regulation of the stomach

This is a complex process that involves positive feedback in the secretion of gastric juice and a negative feedback mechanism that inhibits its secretion. Secretion of **histamine** (produced directly and stimulated by the hormone gastrin) is the significant positive mechanism in the secretion of acid in the stomach. However, acid secretion is inhibited by the gastrointestinal hormone somatostatin. These are summarized in the three key steps:

Cephalic ('in the head') phase
Sensations of smell, taste or food thought directs nerve impulses (action potentials) to the brain which stimulates secretions of gastric acid and the enzyme pepsin in the stomach. The presence of the carbonic acid/hydrogen carbonate, H_2CO_3/HCO_3^- buffer system ensures the pH of gastric juice remains in a safe range. The food sensation also discharges the hormone gastrin which travels through the blood and further stimulates the secretion of hydrochloric acid and pepsin through production of **histamine** (a 'local' hormone).

Gastric phase
When food enters the stomach, it is stretched beyond its normal dimension (called distension). This results in further secretion of hydrochloric acid and pepsin.

Intestinal phase
Partly liquid digested food enters the small intestine and when pH reaches below 2, gastric secretion is inhibited by negative feedback in several different ways: H^+ (aq) ions (and lipids) trigger impulses to the brain that reduce stimulation of gastric glands; reflex action of H^+ (aq) ions on the gut wall decreases gastric secretions and somatostatin is released into the blood to the gastric glands that also inhibits acid secretion.

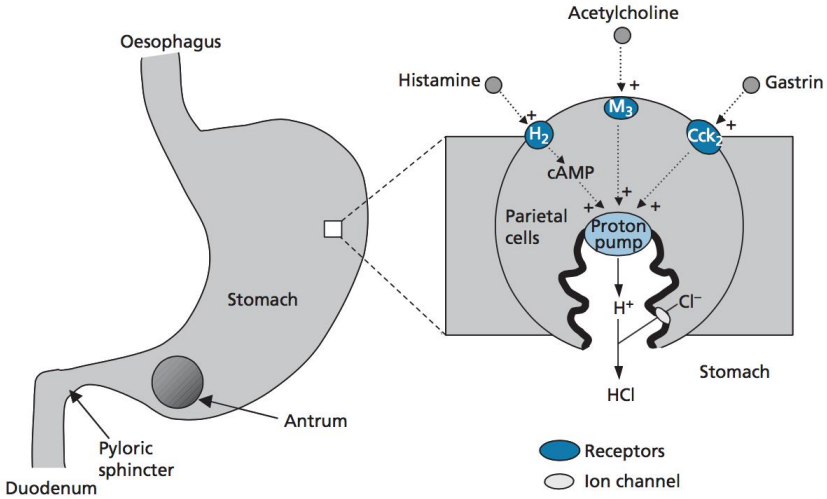


Figure 4.3 Factors influencing the release of gastric acid (hydrochloric acid); acetylcholine is a neurotransmitter

Specific inhibition of hydrochloric acid production in the stomach

Excessive production of hydrochloric acid can be inhibited using drugs, such as ranitidine (Zantac), which acts as an **antagonist** of the histamine-H_2 protein receptor on parietal cells, which is responsible for promoting hydrochloric acid production. When it binds to the H2-receptort it stops the naturally occurring histamine molecule (the **agonis**t) from binding.

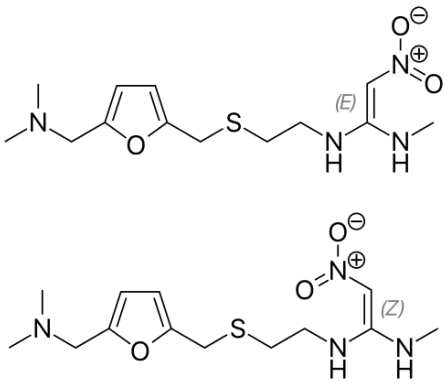


Figure 4.4 Structure of ranitidine (Zantac)

The design of **H_2 antagonists**, such as ranitidine (Zantac) was based on the natural agonist histamine as a lead compound. Chain extension accessed an antagonist binding region, and the replacement of an ionized terminal group with a polar, un-ionized group capable of hydrogen bonding led to pure antagonists.

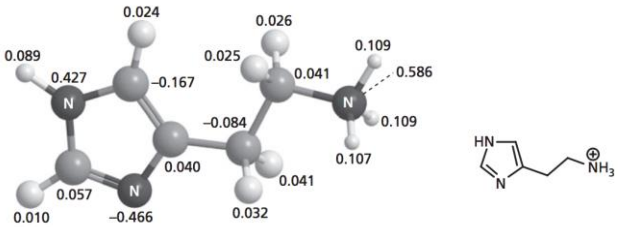


Figure 4.5 Charge distribution on the histamine ion (stabilized by resonance) – the numbers indicate the average charges on the atoms

Until the 1970's drug design was often a hit and miss affair where the emphasis was on synthesizing as many analogues of the lead compound as possible. Since the 1980's the emphasis has been on rational drug design based on an understanding of the drug's mechanism of action and its target structure.

Activity 4.4
What type of isomerism is ranitidine (Zantac) exhibiting? Explain the origin of this isomerism.

Answer:
Geometric (cis/trans) isomerism; restricted rotation around a carbon-carbon double bond.

Proton (H^+) pump inhibitors were the next step in drug development to reduce acid secretion in the stomach and tests have shown that they are very effective compared to Zantac and placebos. They work by inhibiting the H^+-K^+-ATPase enzyme, a membrane-based protein that uses ATP (a short term form of chemical energy in cells) to pump acid (protons) into the stomach.

Omeprazole (Prilose™ or Losec™) is a well-known example of this type of drug. It is a substituted benzimidazole and binds to a specific amino acid of the enzyme, forming a covalent disulfide link and thereby inhibiting acid secretion.

Omeprazole is a racemic mixture of two enantiomers. It is optically active because the molecule is chiral due to the presence of three different substituents and a lone pair of electrons on the chiral sulfur atom. They are mainly in the un-ionized form at the pH of the blood plasma. The structure shown is lipid soluble so that it can pass through the cell membrane of the parietal cells.

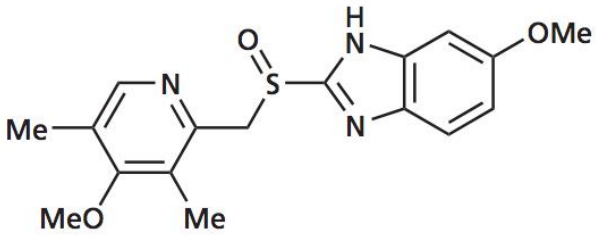


Figure 4.6 Structure of omeprazole (Me= methyl group, $-CH_3$)

Omeprazole exists as two enantiomers. The R-form is inactive, though it converts into the active S-enantiomer *in vivo* (in the body). The pharmaceutical company Astra Zeneca sells the S isomer drug as Nexium (esomeprazole).

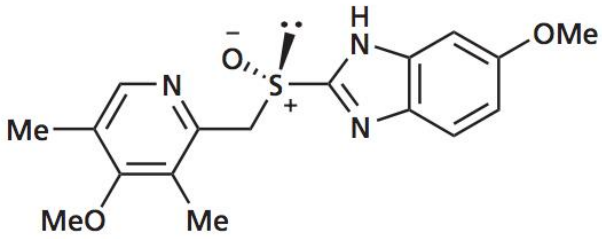


Figure 4.7 Structure of esomeprazole

In contrast to many drugs, both enantiomers of omeprazole show very similar pharmacological properties. In their original forms (known as pro drugs) they are biologically inactive and do not interact with the gastric proton pump directly. It has been found that proton pump inhibitors, such as Omeprazole have an inherent anti- *H. pylori* action and it has been suggested that they inhibit urease. This anti- bacterial activity is sufficient to suppress the bacterium but not eradicate it, so traditional antibacterial agents (antibiotics) are still required.

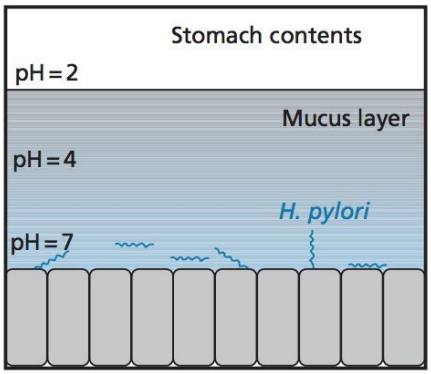
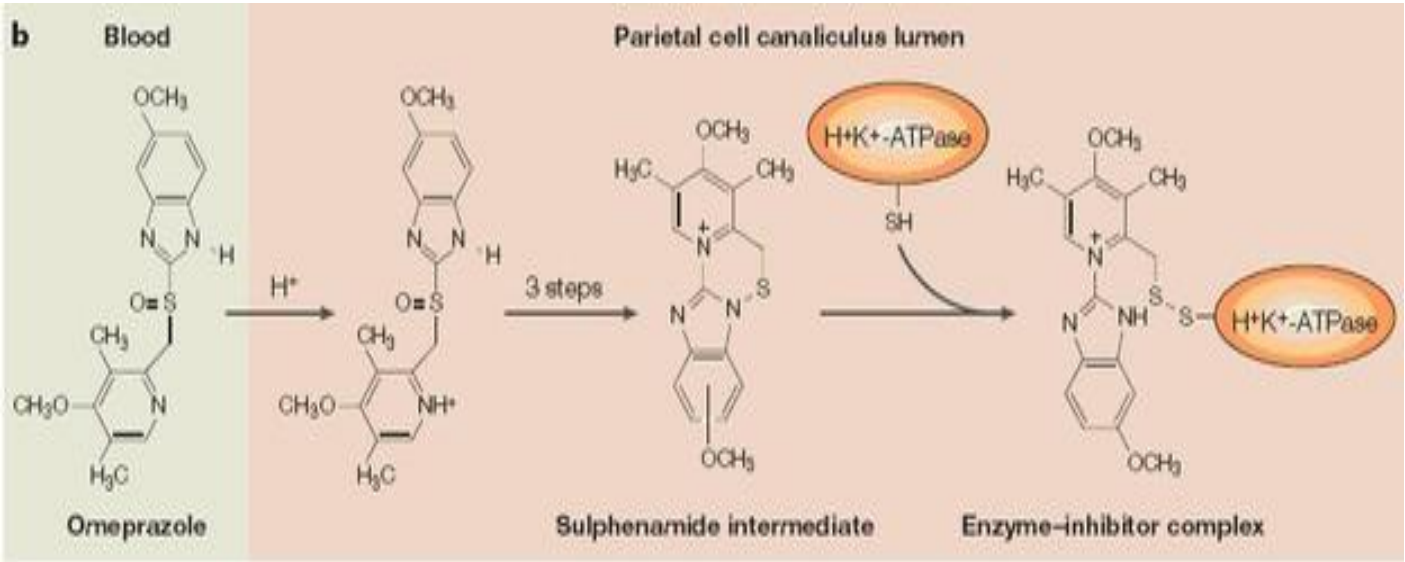


Figure 4.8 *H. pylori* attached to stomach cells

Due to their low polarity, omeprazole and esomeprazole readily cross the lipid bilayer of cell membranes and enter the cytoplasm of parietal cells containing hydrochloric acid. In this acidic environment near the parietal cell surface both enantiomers undergo a series of acid-catalysed chemical changes and produce the same **active metabolites**, which bind to the proton pump of the parietal cell (via a sulfur-sulfur bridge) and inhibit the section of hydrochloric acid.

Omeprazole becomes ionized when the weak base molecule is protonated and hence unable to cross back into the cell through the cell membrane. This mechanism of action increases the efficiency and bioavailability of both drugs and allows a reduced frequency of administration. Omeprazole and proton pump inhibitors have very few side effects because of their selectivity and mechanism of action. The drugs are effective for an extended period of time until the cell is able to synthesize new proton pumps.



Buffers

A buffer solution is an aqueous solution whose pH (and hence hydrogen ion concentration) remains unchanged by dilution with water or when relatively small amounts of acid or alkali are added to it. Buffers *resist* changes in pH. Physiological systems, such as blood and gastric juice, are buffered; the action of enzymes is heavily pH dependent.

Types of buffers

There are two types of buffer: acidic buffers, consisting of a weak acid and its conjugate base, for example, ethanoic acid and sodium ethanoate and basic or alkaline buffers, which are prepared from a weak base and its conjugate acid, for example, aqueous ammonia and ammonium chloride.

Action of a buffer

Acidic buffers

Since ethanoic acid is only slightly dissociated and sodium ethanoate is completely dissociated, a mixture of the two contains a relatively low concentration of hydrogen ions, but a large proportion of ethanoic acid molecules and ethanoate ions:

$CH_3COONa(aq) \rightarrow CH_3COO^-(aq) + Na^+(aq)$

$CH_3COOH(aq) \rightleftharpoons CH_3COO^-(aq) + H^+(aq)$

If a small volume of an acid is added to the buffer, the additional hydrogen ions (extra H^+) will be removed by combination with the ethanoate ions to form undissociated acid molecules. The presence of sodium ethanoate ensures there is a large ‘reservoir’ of ethanoate ions to ‘mop up’ the additional hydrogen ions from an acid.

If an alkali is added, the hydroxide ions combine with the hydrogen ions to form water molecules:
$H^+(aq) + OH^-(aq) \rightarrow H_2O(l)$.
Overall reaction: $CH_3COOH\ (aq) + OH^-\ (aq) \rightarrow\ CH_3COO^-\ (aq) + H_2O\ (l)$.

The removal of hydrogen ions via neutralization with ethanoic acid results in the dissociation of the weak acid molecules to replenish the hydrogen ions removed. The presence of ethanoic acid ensures that there is a large ‘reservoir’ of un-dissociated ethanoic acid molecules that will dissociate following the addition of an alkali. Hence, the pH changes very slightly.

Basic buffers

Since ammonia is only slightly dissociated and ammonium chloride is completely dissociated, a mixture of the two contains a relatively low concentration of hydroxide ions, but a large proportion of ammonia molecules and ammonium ions (conjugate acid):

$NH_4Cl(aq) \rightarrow NH_4^+(aq) + Cl^-(aq)$
$NH_3(aq) + H_2O(l) \rightleftharpoons NH_4^+(aq) + OH^-(aq)$
If an acid is added, the hydrogen ions will combine with hydroxide ions to form water:

$H^+(aq) + OH^-(aq) \rightarrow H_2O(l)$

As a result more ammonia molecules react accept the proton (H^+) from water molecules.

If an alkali is added, the hydroxide ions react with the ammonium ions from ammonium chloride to form ammonia and water. The presence of ammonium chloride ensures that there is a large 'reservoir' of ammonium ions (conjugate acid) to resist changes in pH with the addition of an alkali.

Preparing buffers

The most common preparation method for an acidic buffer solution is combining a weak acid with its conjugate base. The conjugate base comes from an aqueous salt which dissociates in water to give the base. A basic buffer solution can be prepared by combining a weak base with its conjugate acid.

An alternative approach to making an acidic buffer solution is start with a weak acid and add half as many moles of strong base. A basic buffer can also be prepared by starting with a weak base and adding half as many moles of a strong acid.

The issue with any of the above preparation methods is that the initial solution is a weak acid or weak base, otherwise the starting acid or base would already be 100% dissociated or ionized. Both components of a conjugate acid-base pair must remain in the solution to be able to neutralize any added acid or base. Regardless of the method of buffer production, the nature of the acid-base buffer always remains the same – a constant pH is maintained following the additions of small volumes of acid or base.

Buffer calculations

The pH of a buffer solution can be calculated with the logarithmic form of the equilibrium law applied to the dissociation of a weak acid:

$$pH = pK_a + \log_{10} \frac{[conjugate\ base]}{[conjugate\ acid]}$$

This expression is known as the **Henderson–Hasselbalch equation**.

Derivation of the Henderson-Hasselbach equation

Consider the equilibrium for a weak acid, H-A:

$HA(aq) \rightleftharpoons H^+(aq) + A^-(aq)$; $K_a = \frac{[H^+(aq)] \times [A^-(aq)]}{[HA(aq)]}$

Rearranging:

$[H^+(aq)] = \frac{K_a \times [HA(aq)]}{[A^-(aq)]}$

Taking negative logarithms to the base 10 of both sides:

$pH = pK_a - \log_{10} \frac{[HA(aq)]}{[A^-(aq)]}$ or $pH = pK_a + \log_{10} \frac{[A^-(aq)]}{[HA(aq)]}$

The buffer will be most effective when the concentration of the weak acid is equal to the concentration of the salt of the weak acid.

Calculations with the Henderson–Hasselbalch equation may require conversions involving H^+ and pH; K_a and pK_a and calculations of concentrations from masses of pure substances and volumes of solutions.

Diluting a buffer solution with water does not change the ratio of the concentrations of the salt and acid so the pH does not change (unless the dilution is so great that the assumptions made when deriving the equation no longer apply).

Two assumptions are made to simplify calculations involving buffers solutions: In the buffer solution, the weak acid or weak base is not dissociated. This is because the presence of ions from the dissociation of its salt will prevent dissociation of the acid or base molecules. In the buffer solution, it is assumed that all the ions present in the solution are produced by the dissolution of the salt: a negligible amount originates from the acid or base.

Activity 4.5

Calculate the pH of a buffer containing 0.20 moles of sodium ethanoate in 500 cm^3 of 0.10 mol dm^{-3} ethanoic acid. K_a for ethanoic acid is 1.8×10^{-5} mol dm^{-3}.

Activity 4.5 answer

$[CH_3COO^-(aq)] = 0.20 \times \frac{1000}{500} = 0.40$ mol dm^{-3}

$\frac{[H^+(aq)] \times [CH_3COO^-(aq)]}{[CH_3COOH(aq)]} = 1.8 \times 10^{-5}$

$1.8 \times 10^{-5} = \frac{(x)' (0.40)}{0.10}$

$x = 4.5 \times 10^{-6} = [H^+(aq)]$

$pH = -\log_{10}[H^+(aq)] = -\log_{10}(4.5 \times 10^{-6}) = 5.3$

Buffer capacity

Buffer solutions have a limited capacity to resist pH changes. If too large a volume of strong acid or strong base is added no more buffering action is possible.

For example, consider a buffer composed of ethanoic acid (a weak acid) and sodium ethanoate (conjugate base). (Remember weak acids have strong conjugate bases).

Consider the addition of a strong acid such as HCl to a buffer composed of ethanoic acid and sodium ethanoate.

Initially, the HCl donates its proton to the conjugate base (CH_3COO^-) through the reaction $CH_3COO^- + HCl \rightarrow CH_3COOH + Cl^-$. This changes the pH by lowering the ratio $[CH_3COO^-]/[CH_3COOH]$, but if there is still a lot of CH_3COO^- present, the change in pH will be relatively small (see below for a worked example).

But if we keep adding HCl, the conjugate base CH_3COO^- will eventually run out. Once the CH_3COO^- is gone, any additional HCl will donate its proton to water ($HCl + H_2O \rightarrow H_3O^+ + Cl^-$). This will dramatically increase the concentration $[H_3O^+]$ and so the pH decreases significantly.

We call this 'breaking the buffer solution', and we call the amount of acid a buffer can absorb before it breaks the 'buffer capacity for addition of strong acid'. A solution of this buffer with more conjugate base, $[CH_3COO^-]$, has a higher buffer capacity for addition of strong acid.

Similarly, a buffer will 'break' when the amount of strong base added is so large it consumes all the weak acid, through the reaction
$CH_3COOH + OH^- \rightarrow CH_3COO^- + H_2O$. A solution with more weak acid, $[CH_3COOH]$, has a higher buffer capacity for addition of strong base.

So, although the pH of this buffer is determined by only the ratio $[CH_3COO^-]/[CH_3COOH]$, the ability of the buffer to absorb strong acid or base is determined by the individual concentrations of $[CH_3COO^-]$ and $[CH_3COOH]$.

Calculating changes in the pH of buffer solutions

Calculate the change in pH when (1.0 cm^3) of 1.0 mol dm^{-3} NaoH is added to a 1.0 dm^3 buffer solution which contains a mixture of 0.10 mol dm^{-3} CH_3COOH and 0.10 mol dm^{-3} CH_3COONa (pK_a CH_3COOH = 4.75).

Applying the Henderson-Hasselbach equation:

pH of the buffer solution before adding NaOH: pH = 4.5 + $\log_{10}\frac{0.10}{0.10}$ = 4.75

Amount of OH^- ions added = $1 \times \frac{1}{1000}$ =10^{-3} mol

$CH_3COOH + OH^- \rightarrow CH_3COO^- + H_2O$

[CH_3COOH] after the addition of the NaOH = 0.10 - 10^{-3} = 0.099 mol dm^{-3}

[$CHCOO^-$] after the addition of the NaOH = 0.10 + 10^{-3} = 0.101 mol dm^{-3}

pH = pK_a + $\log_{10}\frac{0.101}{0.099}$ = 4.76

Change in pH = 0.01, thus the addition of a small amount of alkali to a buffer solution causes only a very small change in the pH of the buffer solution.

Activity 4.6

Calculate the mass of sodium propanoate (M = 96.07 g mol^{-1}) that must be dissolved in 1.00 dm^3 of 1.00 mol dm^{-3} propanoic acid (pK_a = 4.87) to give a buffer solution with a pH of 4.5. (Let x represent the concentration of propanoate ions and y represent the amount of sodium propanoate.)

Activity 4.6 answer

$[H^+(aq)] = 10^{-pH} = 1 \times 10^{-4.5} = 3.16 \times 10^{-5}$ mol dm^{-3}
$K_a = 1 \times 10^{-4.87} = 1.35 \times 10^{-5}$
$K_a = \frac{[H^+(aq)][CH_3CH_2COO^-(aq)]}{[CH_3CH_2COOH(aq)]}$ = 1.35 × 10^{-5}; 1.35 × 10^{-5} = $\frac{(3.16 \times 10^{-5})(x)}{1.00}$
x = 0.427 mol dm^{-3}; 0.427 mol dm^{-3} = $\frac{y}{1.00\,dm^3}$
y = 0.427 mol; 96.07 g mol^{-1} × 0.427 mol = 41.0 g

Activity 4.7

Calculate the pH of a standard solution containing 0.20 mol dm^{-3} HF (aq) and 0.40 mol dm^{-3}, KF (aq). The K_a for hydrofluoric acid is 6.8×10^{-4} mol dm^{-3}.

Activity 4.7 answer

$pH = pK_a + \log_{10}$ [salt]/[acid]; $pH = -\log_{10}(6.8 \times 10^{-4}) + \log_{10}(0.4)/(0.2) = 3.47$

Hydrogencarbonate and carbonate buffers (in the body)

Blood is a complex liquid that contains cells suspended in plasma, which contains various ions and molecules dissolved in water. These dissolved solutes in blood contain buffer systems which regulate the body pH to a constant value of 7.4.

The main buffer system in blood consists of carbonic acid, H_2CO_3 (aq), hydrogen carbonate ions, HCO_3^- (aq), and carbon dioxide, CO_2 (aq). Carbon dioxide is produced by the respiration (oxidation) of glucose in all body tissues. The carbon dioxide released by respiration diffuses out of the body cells into the blood and is transported in the plasma to the lungs, where it is exhaled (breathed out).

The following equilibria are responsible for the buffering action of the carbonic acid-hydrogencarbonate ion buffer. The equilibrium constants for reactions 1, 2 and 3 are K_1, K_2 and K_3, respectively:

1. H_2CO_3 (aq) + H_2O (l) ⇌ H_3O^+ (aq) + HCO_3^- (aq); K_1
2. CO_2 (aq) + H_2O (l) ⇌ H_2CO_3 (aq); K_2
3. CO_2 (g) ⇌ CO_2 (aq); K_3
4. CO_2 (g) + $2H_2O$ (l) ⇌ H_3O^+ (aq) + HCO_3^- (aq); $K_1 \times K_2 \times K_3 = K_4$

The overall reaction represented by equation 4 indicates that the concentration of oxonium ions, H_3O^+ (aq), and the pH of blood depend only on the concentration of hydrogen carbonate ions dissolved in blood and on the partial pressure of gaseous carbon dioxide, CO_2 (g), in the air spaces in the lungs.

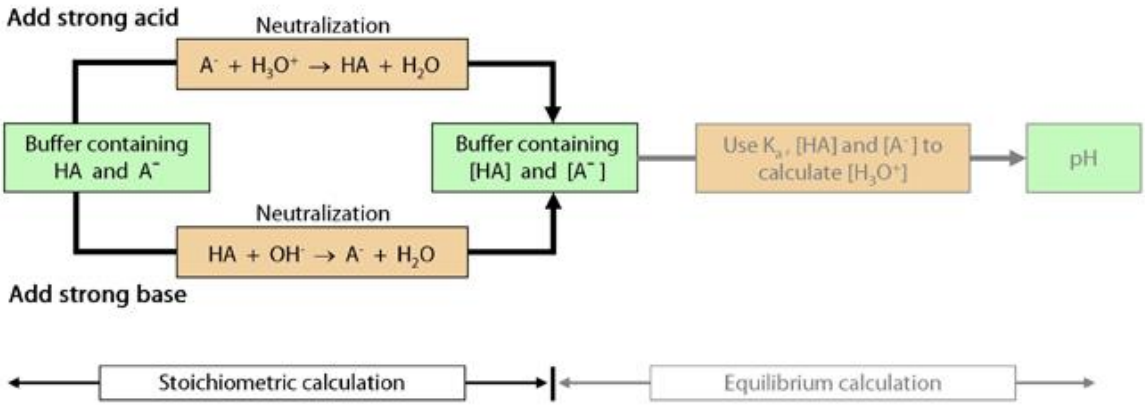
Activity 4.8

0.10 mol of solid sodium hydrogen carbonate and 0.20 mol of solid sodium carbonate are dissolved in the same beaker of water, transferred to a volumetric flask and made to 250.0 cm^3. The K_a for the hydrogen carbonate ion, HCO_3^-, is 4.7×10^{-11}. Determine the pH of the resulting buffer.

Activity 4.8 answer

$pH = pK_a + \log_{10}([A^-]/[HA]) = -\log_{10}(4.7 \times 10^{-11}) + \log_{10}(0.2/0.1) = 10.6$

Summary of how buffers work



D5. Antiviral medications

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

Understandings:

- Viruses lack a cell structure and so are more difficult to target with drugs than bacteria.
- Antiviral drugs may work by altering the cell's genetic material so that the virus cannot use it to multiply. Alternatively, they may prevent the viruses from multiplying by blocking enzyme activity within the host cell.

Applications and skills:

- Explanation of the different ways in which antiviral medications work.
- Description of how viruses differ from bacteria.
- Explanation of how oseltamivir (Tamiflu) and zanamivir (Relenza) work as a preventative agent against flu viruses.
- Comparison of the structures of oseltamivir and zanamivir.
- Discussion of the difficulties associated with solving the AIDS problem.

Guidance

- Structures for oseltamivir and zanamivir can be found in the data booklet in section 37.

Bacteria

Bacteria are single-celled (unicellular) microorganisms that reproduce outside cells by binary division (a form of asexual reproduction). Bacterial cells are too large to enter human cells. They do not contain a nucleus and are known as prokaryotes.

Bacteria can exchange genetic material during a sexual process called conjugation (involving the pili) and acquire genes for antibiotic resistance. There is no nuclear membrane surrounding their DNA and no membrane bound structures within their cytoplasm. They have a protective cell wall and some species have a rotating flagellum for movement. The cell capsule is a polysaccharide layer that provides the bacterium protection against the immune system and prevents dehydration.

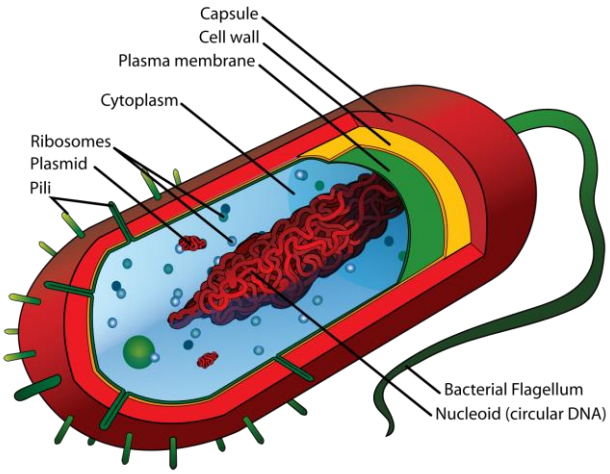


Figure 5.1 The structure of *Escherichia coli* – a 'typical' bacterium

Viruses

Viruses contain DNA or RNA surrounded by a capsid composed of regularly packed capsomeres, each containing a number of protein molecules. Some viruses, such as HIV, have a cell membrane formed from their host cell. Viruses are non-cellular: there is no nucleus or cytoplasm. They can only replicate inside living cells. They are typically 100 smaller at least then bacteria and cannot be seen with a light microscope.

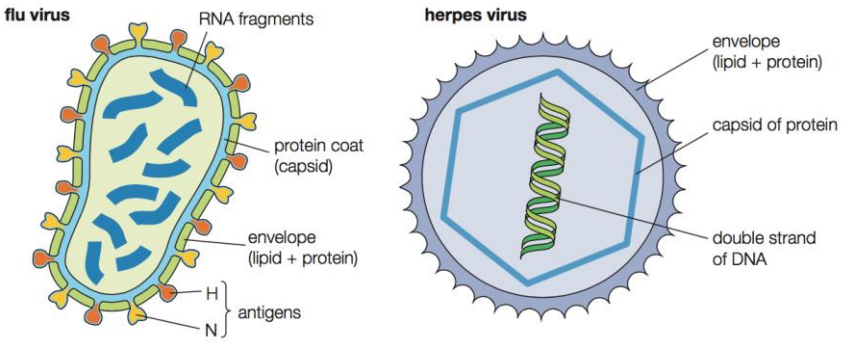


Figure 5.2 The structures of the flu and herpes viruses

An antigen is any substance that causes your immune system to produce antibodies against it. Once a virus or its nucleic acid enters a cell the host cell's enzymes and ribosomes (are used to make new viral proteins and enzymes that self-assemble into viruses. The viruses will then exit from the cell through the cell membrane, leaving behind a dead or damaged cell.

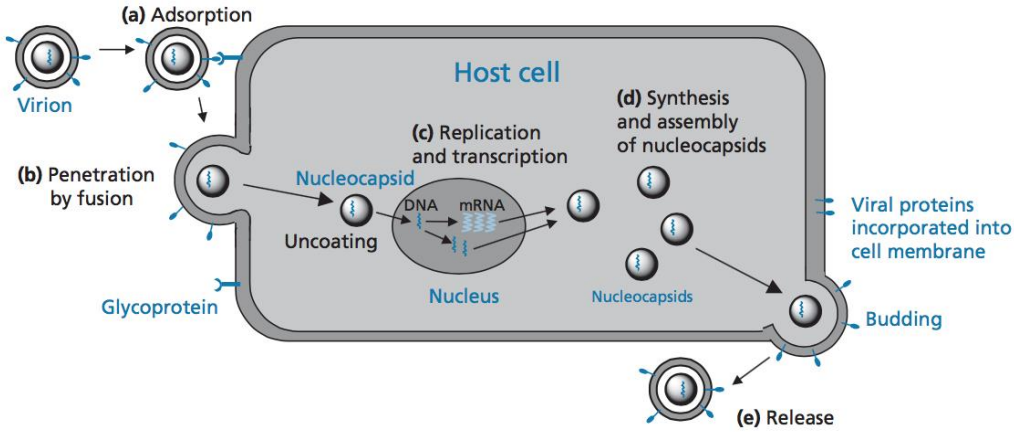


Figure 5.3 Invasion of a DNA virus

Life cycle of a DNA virus such as herpes simplex: a glycoprotein is a protein with a covalently attached sugar resides; the nucleocapsid is a unit of viral structure, consisting of a capsid with the enclosed nucleic acid; a virion is a mature virus particle. Messenger RNA is in effect a copy of the DNA used as a 'template' to make proteins.

Ribosomes are structures found in all cells and are involved in protein synthesis. They may be free in the cytoplasm or associated with internal membranes (except in bacteria). Some antibiotics (see section D.2), such as erythromycin, function by inhibiting bacterial ribosomes. Viruses do not contain ribosomes.

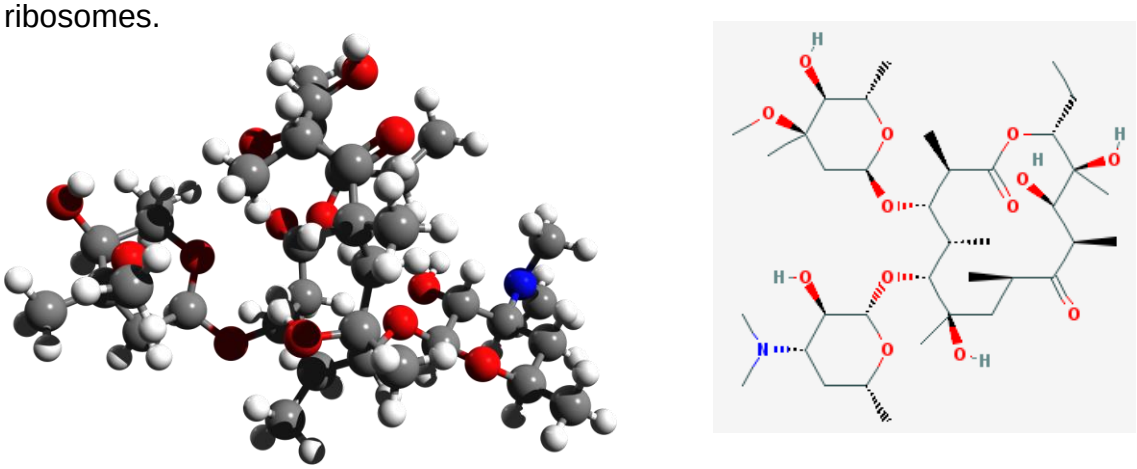


Figure 5.4 Structure of erythromycin ($C_{37}H_{67}NO_{13}$)

Antibiotics are ineffective against viral infections, but may be prescribed to prevent a secondary bacterial infection during a viral infection.

HIV virus

In many RNA and DNA viruses, such as flu and herpes, nucleic acid replication occurs entirely in the cytoplasm.

However, in retroviruses, such as HIV, their RNA is used as a template for making viral DNA, using a viral enzyme called reverse transcriptase. In viral infections involving retroviruses, the viral DNA becomes integrated into the host's DNA and may not kill the host or cause any obvious illness.

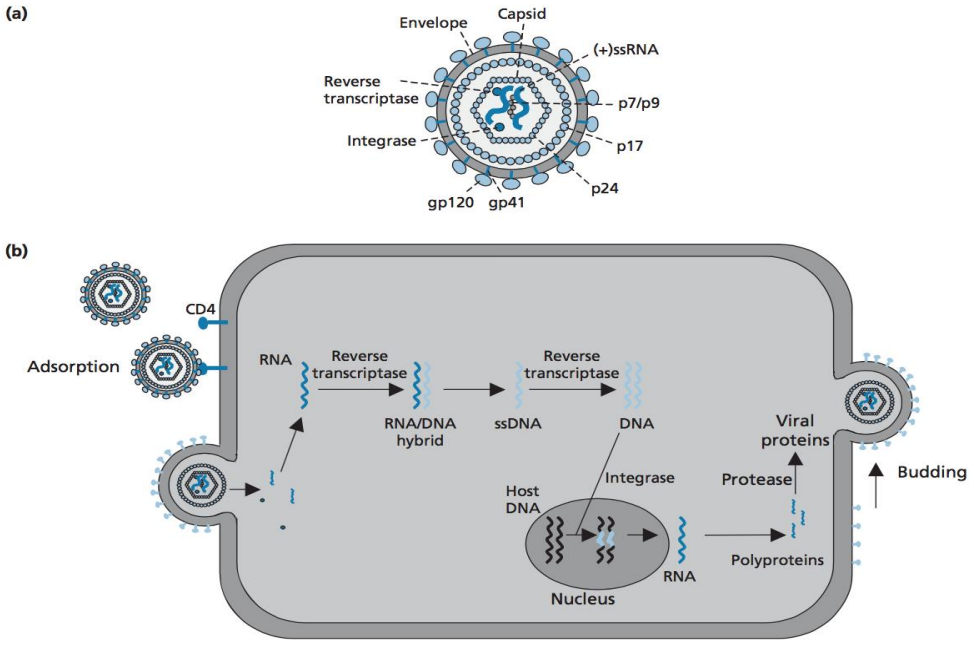


Figure 5.5 (a) Structure of HIV particle (p = protein; gp = glycoprotein) and (b) life cycle of HIV in a host T-cell.

CD4 (cluster of differentiation 4) is a glycoprotein found on the surface of immune cells such as T helper cells (important regulatory cells in the immune system). Retroviral integrase is an enzyme produced by a retrovirus, such as HIV that enables its genetic material to be integrated into the DNA of the infected cell.

HIV-1 protease is a protease that is essential for the life-cycle of HIV. HIV protease cleaves newly synthesized proteins the appropriate places to create the mature protein components of an infectious HIV virion. Without effective HIV protease, HIV virions remain uninfectious.

The table below shows some of the differences and similarities between bacteria and viruses.

	Bacteria	**Viruses**
Ribosomes	Present	Absent
Number of cells	Unicellular; one cell (but can form cooperating colonies)	No cells (acellular);
Internal structure	DNA floating freely in cytoplasm. Has cell wall and cell membrane	DNA or RNA enclosed inside a coat (capsid) of protein or glycoproteins,
Cell wall composition	Peptidoglycan/lipopolysaccharid	No cell wall. Protein coat (capsid) present inste
Treatment	Antibiotics	Vaccines prevent the spread of infections and antiviral medications help to slow replication but cannot stop it completely.
Enzymes	Yes	Yes, in some, for example, reverse transcriptas Retroviruses.
Nucleus	No, the nuclear material (nucleoid) is not surrounded by nuclear membrane	No
Virulence	Yes	Yes
Infection	Localized	Systemic
Reproduction	Binary fission- a form of asexual reproduction	Invades a host cell and takes over the cell causing it to make copies of the viral genome (DNA or RNA). Destroys or damages the host releasing new viruses.
Size	Larger (1000nm)	Smaller (20 - 400nm)

Activity 5.1

How would you define 'life'? Are viruses 'alive'? What is their evolutionary relationship with other living organisms? Why does the human genome contain retroviral sequences? Refer to http://www.scientificamerican.com/article/are-viruses-alive-2004/ and http://www.ncbi.nlm.nih.gov/pmc/articles/PMC138943/

Antiviral drugs

In general, there are **four** types of actions for antiviral drugs:

I. Preventing the genetic material from being injected through the cell membrane; viruses must interact and bind with specific receptors (proteins or glycoproteins) on the cell membrane of a cell and release its genetic material.

II. To block entry, antiviral molecules can be synthesized that are structurally similar to the virus-associated protein so they bind strongly to the receptor or even bind to the viral capsid (protein coat). They can also inhibit the uncoating process: the release of viral nucleic acids from the capsid that covers them.

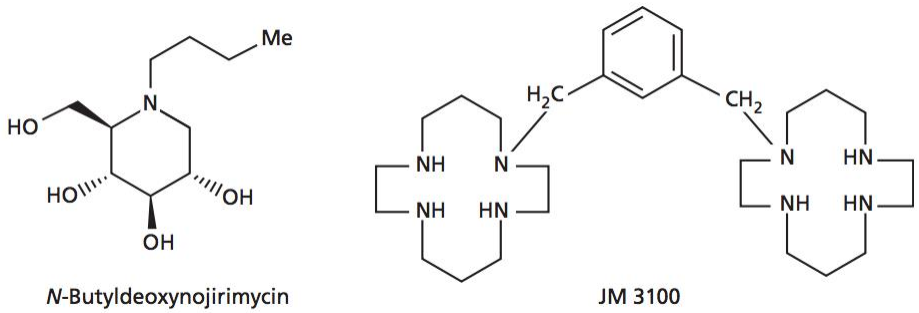


Figure 5.6 Agents that inhibit cell entry

III. Inhibiting the replication of the virus: the drug may mimic nucleotides, the monomers of DNA or RNA, so that they are incorporated into the enzyme-controlled synthesis of DNA or RNA, which is then terminated.

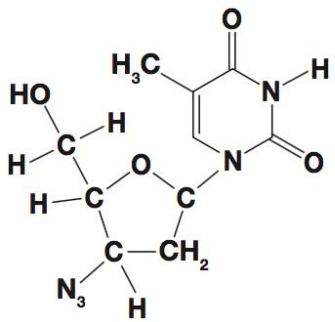


Figure 5.7 Structure of azidothymidine (AZT) or Zidovudine used in the clinical treatment of AIDS

Inhibiting the action of reverse transcriptase present in retroviruses, for example HIV.

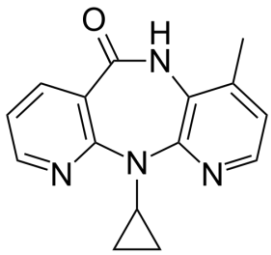


Figure 5.8 Nevirapine, non-nucleotide reverse transcriptase inhibitor for treatment of HIV infection

IV. Preventing new viruses from leaving the cell: new DNA and viral proteins self-assemble into new viruses (viral particles). Following rupture of host cell membranes (or budding), these viruses leave the host cell; this then results in new infections in other cells of the body. Drugs may be developed that prevent the exit of the mature viruses (virions).

Designing safe and effective antiviral drugs is difficult, because viruses use the host's cells to replicate. This makes it difficult to find targets for the drug that would interfere with the virus without also harming the host organism's cells. The major problem in developing vaccines and anti-viral drugs is due to viral variation and rapid evolutionary change.

HIV therapy

There is no effective vaccine and no cure. Current anti-viral drugs for treating HIV slow down the replication rate of the HIV virus. A mixture (‘cock tail’) of antivirals is most effective in managing HIV infection. Retroviruses, such as HIV, have a higher mutation rate than DNA viruses which impedes development of vaccines and drugs. Preventing infection by the use of condoms is the most effective method for reducing HIV infection rates. However, HIV is also transmitted by blood and can pass from an infected mother to her baby. AIDS related deaths have had a significant impact on life expectancy and the cause of many social problems, for example, orphans and shunning of HIV positive people and economic, for example, loss of economically productive people from the job market.

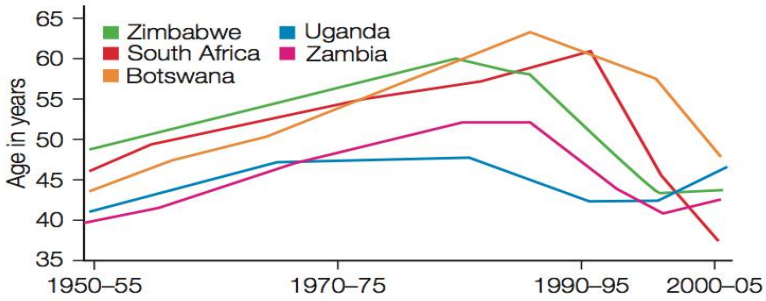


Figure 5.9 AIDS in Africa: life expectancy in selected African countries

Oseltamivir and zanamivir

Oseltamivir (Tamiflu) and zanamivir (Relenza) are two anti-viral drugs specifically designed to treat the flu, caused by the influenza A and B viruses. Oseltamivir is taken orally and zanamivir is inhaled as a dry powder.

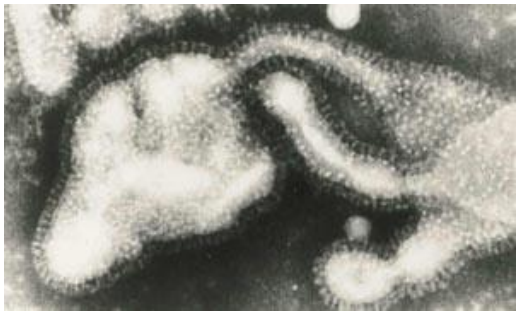
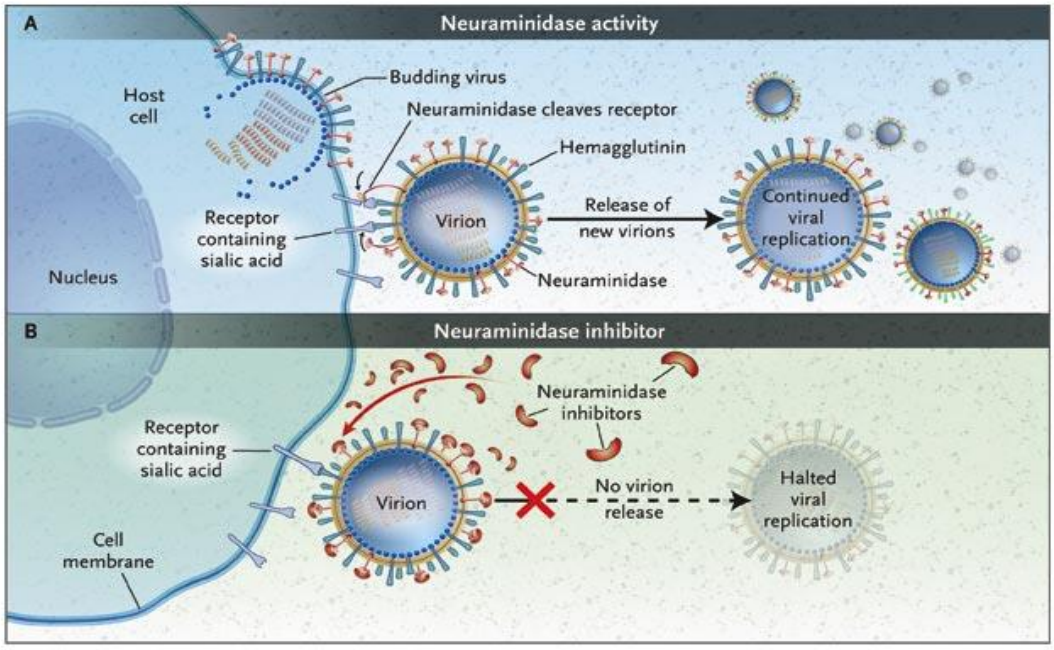


Figure 5.10 Electron micrograph of flu virus

The prodrug oseltamivir is itself not virally effective; however, once in the liver it is hydrolysed to its active metabolite - the free oseltamivir carboxylate.

Oseltamivir and zanamivir are neuraminidase inhibitors, acting as a competitive inhibitor of the activity of the viral neuraminidase enzyme upon sialic acid, found on glycoproteins on the surface of the host cells. Haemagglutinin is a glycoprotein found on the surface of flu viruses. It is responsible for binding the virus to cells with sialic acid on the membranes, such as cells in the upper respiratory tract or erythrocytes



By blocking the activity of the enzyme, oseltamivir and zanamivir prevent new virus particles (virions) from departing the host cell.

Both molecules contain a six-membered ring with three chiral carbon atoms (marked with asterisks). Both drugs engage in a variety of favorable interactions, including hydrogen bonding and ionic interactions with the active site of neuraminidase.

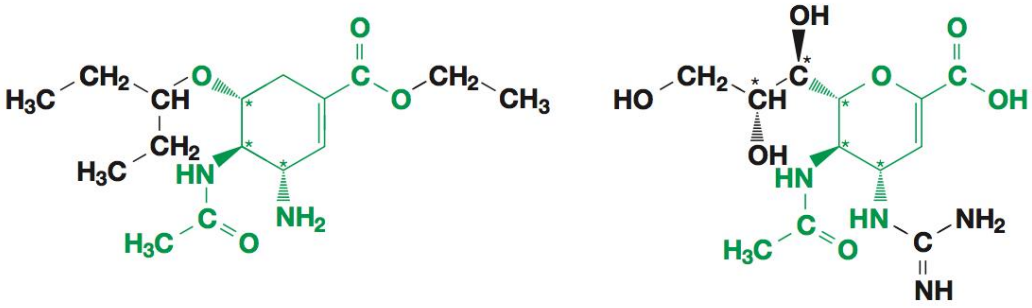


Figure 5.11 The structures of oseltamivir and zanamivir (the chiral carbon atoms are marked with *).

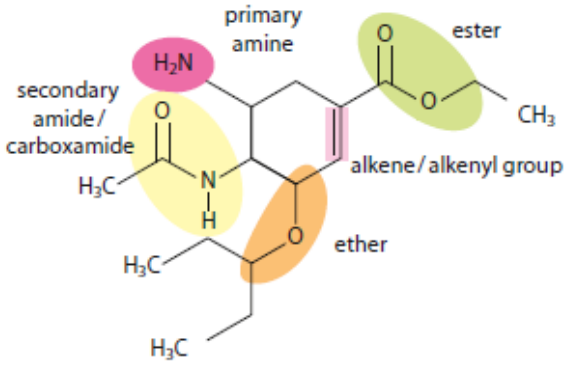
Activity 5.2

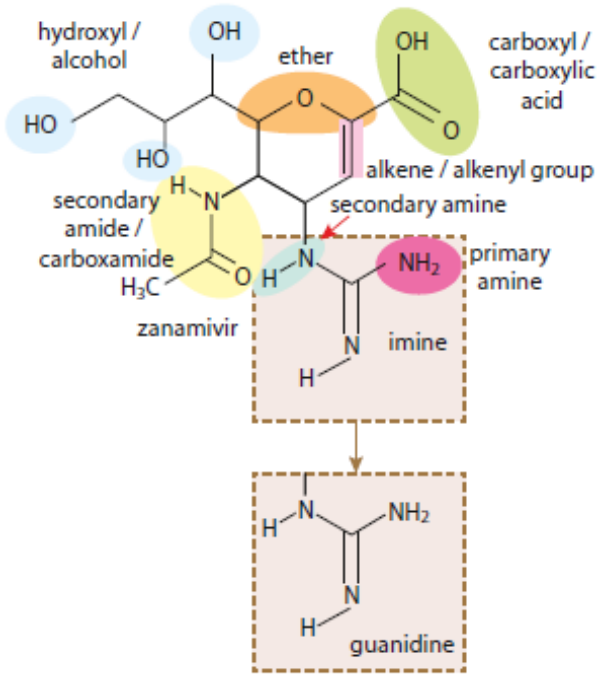
Compare the structures of oseltamivir and zanamivir shown above. Name the functional groups.

Zanamivir contains a number of polar hydroxyl and amine groups together with an ionizable carboxylic acid group which make it more soluble in water than oseltamivir. Oseltamivir has an ester group which renders it inactive in its original form.

Figure 5.12 Tamiflu, can be used as an early preventive measure during flu outbreak

Activity 5.2 Answer





D6. Environmental impact of some medications

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

Understandings

- High-level waste (HLW) is waste that gives off large amounts of ionizing radiation for a long time.
- Low-level waste (LLW) is waste that gives off small amounts of ionizing radiation for a short time.
- Antibiotic resistance occurs when micro-organisms become resistant to anti-bacterials.

Applications and skills:

- Describe the environmental impact of medical nuclear waste disposal.
- Discussion of environmental issues related to left-over solvents.
- Explanation of the dangers of antibiotic waste, from improper drug disposal and animal waste, and the development of antibiotic resistance.
- Discussion of the basics of green chemistry (sustainable chemistry) processes.
- Explanation of how green chemistry was used to develop the precursor for Tamiflu (oseltamivir).

Guidance

- The structure of oseltamivir is provided in the data booklet in section 37.

Radioactive waste

The treatment of cancer (in tumours) often involves radiation therapy (radiotherapy). Ionizing radiation injures or destroys cells in the area being treated by damaging their DNA, making it impossible for these cells to continue to grow and divide.

This may be from an external radioactive source or using radioisotope therapy where a radioisotope is attached to another molecule or antibody, which then guides it to the target tissue after being injected or taken orally.

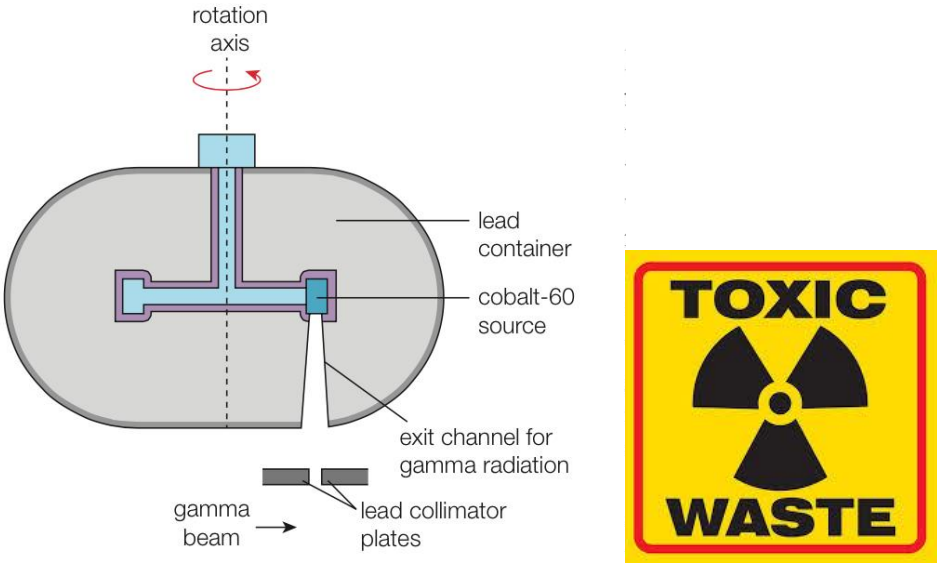


Figure 6.1 Gamma therapy – using gamma rays from cobalt-60 to kill surface tumours

Radioactive waste can be divided into high-level waste (HLW) and low level waste (LLW).

Low-level waste include items such as rubber gloves, syringes, vials, paper towels and protective clothing, such as gloves, that have been used in areas where radioactive materials are handled. Sources of radiation that expose patients to radiation in hospitals include diagnostic medical nuclear procedures, X rays, PET (positron emission tomography) scans, bone scans and thyroid scans.

The level of activity is low and the half-lives of the radioactive nuclides (radioisotopes) are generally short. For example, a fluorine-18 compound is commonly used in a PET scan and has a half-life of only 110 minutes. Iodine-131 has a half-life of 8.0 days and cobalt-60 has a half-life of 5.27 years.

High-level waste has high activity and generally the isotopes have long half-lives (at least hundreds of years) so the waste will remain active for long periods. These wastes produced in nuclear reactors contain a mixture of nuclear fission products with unused nuclear fuel (uranium) Isotopes used in radioisotope therapy tend to be low level waste (typical isotopes used are ^{131}I (used for imaging of the thyroid and treating some types of thyroid cancer) ^{89}Sr (treatment of bone cancer) and ^{153}Sm (used to treat pain when bone cancer has spread).

Any type of radioactive waste needs to be kept separate from other types of waste. LLW is usually disposed of in landfill or in the sea whereas HLW is vitrified (turned into a glass-like material) and buried deep underground in concrete bunkers. LLW will have low activity alpha and low energy beta particles from radioisotopes of short half-lives, whereas HLW will release radiation from high energy beta and gamma emitters. A lot of heat is generated during the decay of the high level nuclear waste and the containers that house the waste before storage need to be cooled.

Nuclear waste can be present in the solid, liquid or gaseous form. If it enters water at the ground level or from the water table, it can enter into and spread through the environment, and enter into food chains through the contaminated water. Radioactive substances can then be passed up the food chain (and sometimes concentrated) via plants to animals and humans. The effects of radiation can be cumulative. Radioactive waste discarded with antibiotic waste can increase the rate of mutation of bacteria and lead to the development of antibiotic resistant bacteria.

Activity 6.1
Deduce the number of protons, neutrons and electrons in an atom of plutonium-240 (formed inside a nuclear reactor).

The three common types of nuclear or ionizing radiation are alpha, beta and gamma radiation. Alpha (α) particles are helium-4 nuclei, $^{4}_{2}He$, that have low penetrating power (a few centimetres of air, depending on their kinetic energy. They are relatively large and slow moving particles (compared to beta particles). They can be stopped by clothing, paper or skin. However, alpha sources can be dangerous if they are in the liquid or gaseous forms since the

radioactive substance may enter the body.

Figure 6.2 International radiation warning symbol

Beta (β) particles (or beta rays) are a stream of high speed electrons (released from nuclei) that have moderate penetrating power (about 100 times greater than the penetrating power of alpha particles). Beta particles can penetrate several metres of air (depending on their kinetic energy) and can be stopped by 1 mm thick aluminium foil. Gamma (γ) rays are high energy photons released from the nucleus. They have a very high penetrating power and can only be stopped by 10 cm of lead or several metres of concrete.

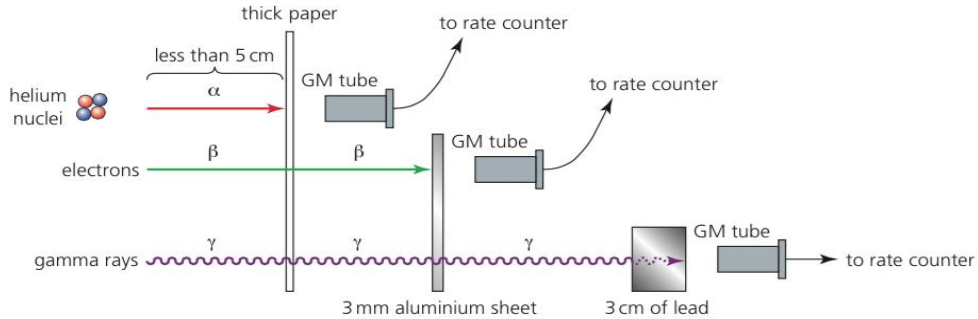


Figure 6.3 Relative penetrating powers of ionizing (nuclear) radiations

Half-life

Some atomic nuclei (nuclides) are very unstable and only exist for a few microseconds, seconds, minutes, hours or days. Others are very stable and take millions of years to decay away to form another atom. Some isotopes are completely stable and do not undergo radioactive decay at all.

The radioactivity (emissions) of any radioactive material always decreases with time. A measure of the stability of a radioisotope is given by its half-life. Unstable nuclei disintegrate at random, you cannot predict which one decay to emit alpha, beta, gamma or other nuclear/ionising radiations. The radioactivity must always decrease over time but never quite reaches zero,

The decay follows are particular pattern, illustrated by the graph below, known as a decay curve. The graph will drop steeply for very unstable nuclei but show a very small gradient if more stable.

The half-life of a radioisotope is the average time it takes for half of the remaining un-decayed radioactive nuclei (atoms) to decay to a different nucleus (atom). It means in one half-life of time, on average, half of the un-decayed unstable nuclei of a particular isotope disintegrate.

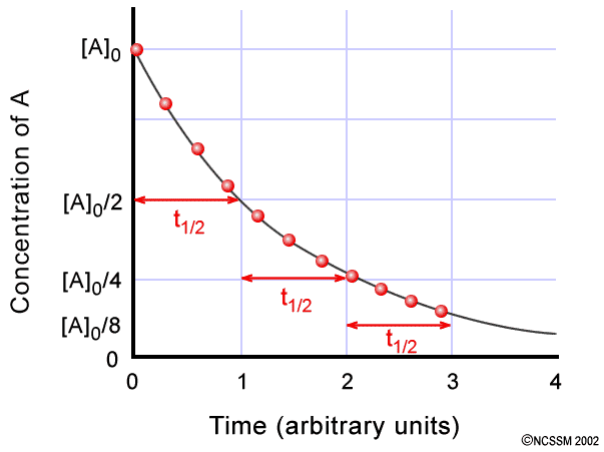


Figure 6.4 Graph showing half-lives

The half-life of a radioisotope has implications about its use and storage and disposal. If the half-life is known then the radioactivity of a source can be predicted in the future. For example, Plutonium-244 produced in the nuclear power industry has a half-life of 40 000 years. Even after 80 000 years there is still a 1/4 of the dangerously radioactive material left. The storage of high level nuclear reactor radioactive waste is going to be quite a costly problem for many (thousands) of years. Storage of high level nuclear waste containing these harmful substances must be stable for hundreds of thousands of years. So there is a storage problem for the 'geological time' future.

Antibiotic waste

Microorganisms in water or the soil can take up waste antibiotics. Bacteria in the organisms can become resistant to antibiotics by a process of natural selection on a bacterial population where there is natural genetic resistance to antibiotics.

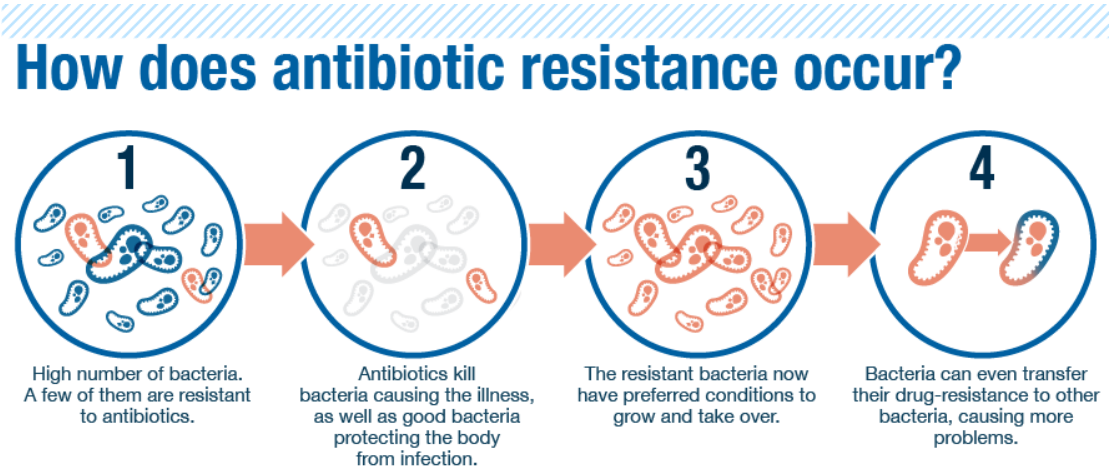


Figure 6.5 Origin of antibiotic resistance

There are high proportions of antibiotic resistance in bacteria that cause common infections (e.g. urinary tract infections, pneumonia, bloodstream infections) in all regions of the world. A high percentage of hospital-acquired infections are caused by highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) or multidrug-resistant Gram-negative bacteria.

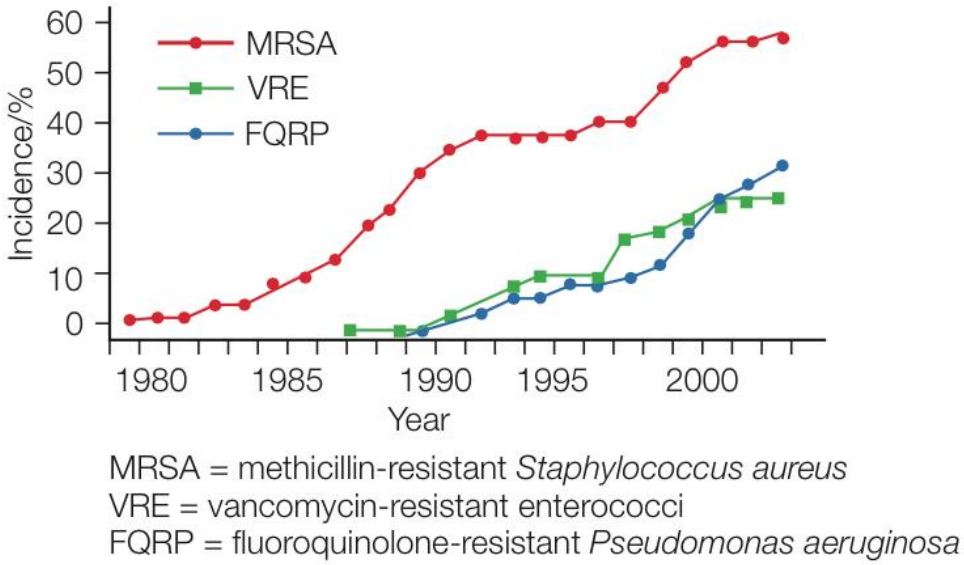


Figure 6.6 Rise of antibiotic resistance in common bacterial infections

If the antibiotic resistant bacteria enters into the potable water supply or food they then make antibiotics much less effective when they are required to treat bacterial infection. Antibiotic waste comes from the disposal of unused antibiotics, through the urine of patients who are on a course of antibiotics and from animals where the feedstock contains antibiotics (to prevent infections in crowded conditions and to improve growth), which often gets discharged into rivers.

Solvent waste

Many different solvents are used in the production of drugs (pharmaceuticals). Solvents are liquids that are used to extract or dissolve other substances. These form a significant proportion of chemical waste. Most industrial solvents used in industry are organic and due to their weak intermolecular forces, they have low boiling points and hence high volatility.

In addition, many solvents are flammable and their vapours may contribute to the greenhouse effect and hence global warming. Chlorinated solvents, such as tetrachloroethene ($Cl_2C=CCl_2$) and dichloromethane (CH_2Cl_2) contribute to ozone depletion. The carbon-chlorine bonds are broken in the presence of ultraviolet radiation (of the appropriate energy) releasing reactive chlorine atoms (free radicals). They are also involved in the formation of hydrogen chloride in photochemical smog.

Many countries have strict guidelines about the safe disposal of organic solvents. They should be separated into chlorine containing (chlorinated) and non-chlorine (non-chlorinated) containing solvents. Chlorinated waste cannot be incinerated with common organic waste because their incomplete combustion could produce highly toxic phosgene ($COCl_2$) and dioxins. To minimize the formation of such by-products, chlorinated solvents must be oxidized separately at very high temperatures or recycled by distillation.

Some of the organic solvents, such as benzene, carbon tetrachloride and chloroform (trichloromethane) are carcinogenic; others are toxic. Health issues from exposure to organic solvents include damage to the skin, eye injury, damage to kidney, liver and reproductive organs, cancer including leukemia and even death.

Environmental problems include pollution of the air, soil and water leading to harmful effects to plants, animals and aquatic organisms. Inorganic acid and alkali solvents are corrosive and cause burns.

Activity 6.2
Draw Lewis structures (electron dot diagrams) for the tetrachloroethene and dichloromethane molecules. Deduce the bond angles and the polarity (if any) of the molecules.

Activity 6.3
Dichloromethane can undergo combustion to form carbon dioxide, water and chlorine, or carbon dioxide and hydrogen chloride. Write balanced equations.

Chlorinated solvents must be incinerated at very high temperature to prevent the formation of carcinogenic dioxins. Non-chlorinated solvents may be recycled (or their solutes such as heavy metals extracted and recycled), burned to provide energy or, if they are innocuous (harmless) such as sodium chloride solution, which can be disposed of in rivers or the sea.

Figure 6.7 Chlorinated solvent in a waste solvent canister

Activity 6.3 answers

$2CH_2Cl_2 + 3O_2 \rightarrow 2CO_2 + 2H_2O + 2Cl_2$.
$CH_2Cl_2 + O_2 \rightarrow CO_2 + 2HCl$

Green chemistry

While the safe disposal of waste with minimal damage to the environment is important, **green chemistry** (also known as sustainable chemistry) aims to reduce harm to the environment by minimizing the use and generation of hazardous chemical substances in the first place.

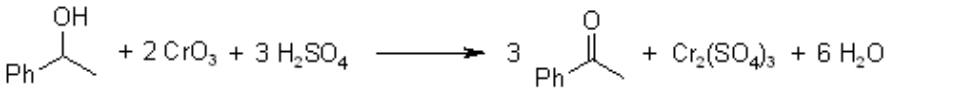
This reduces the pollution at its source and to conserve the Earth's natural (chemical and biological) resources including energy. This is particularly important in the pharmaceutical industry where often the research and development of a new drug involves many steps, each involving many potentially polluting substances, including solvents.

Important factors when designing and producing new drugs include:

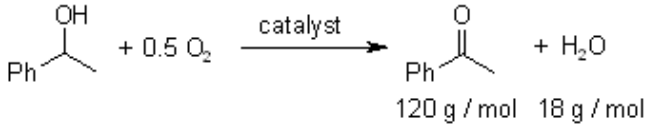
Aiming for a high **atom economy** and low environmental factor. The atom economy is the ratio of the total mass of the desired product (s) to the total mass of all the products. Essentially this is a measure of how much of the reactants remain in the final product.

$$\text{atom efficiency} = \frac{\text{molecular weight of desired product}}{\text{molecular weight of all substances formed}}$$

examples:



$$\text{atom efficiency} = \frac{3 \cdot 120}{3 \cdot 120 + 392 + 6 \cdot 18} = 42\%$$



$$\text{atom efficiency} = \frac{120}{120 + 18} = 87\%$$

The environment factor (E-factor) is defined as the mass of the total waste product divided by the mass of the desired product, which highlights the need to avoid producing waste products.

E = total waste (kg) ÷ mass of desired product (kg)

Pharmaceutical chemistry, where almost all the products contain carbon, also considers the concept of carbon efficiency.

Carbon efficiency = amount of carbon in product ÷ total amount of carbon present in reactants

The number of steps in a multi-step synthesis should be kept to a minimum. Generally the more separate steps required to reach the desired product the lower the percentage yield and the higher the amount of waste reactant and products and the more energy used.

Medicinal chemists will use greener and safer solvents and reactants. Solvents, especially organic solvents, play an important role in many of the separate steps in a synthesis. The energy and materials needed to manufacture the solvent as well as the problems caused by the disposal of the solvents (if they cannot be recycled) all need to be taken into account (in the environmental audit).

In addition, green synthetic chemists will also consider using renewable feed-stocks, using suitable catalysts to reduce energy demands by lowering operating temperature and to consider the fate of the potential drug regarding its breakdown product and disposal after use.

One example of the use of green chemistry in practice is the development of the influenza drug Tamiflu (oseltamivir (see section D5). It acts as an enzyme inhibitor and is an example of rational drug design – meaning its structure was designed to fit the active site of a specific enzyme neuraminidase.

Tamiflu was first synthesized by chemists working at Monash University in Australia. Their technique only produced very small amounts (milligrams) of product and used unsafe lithium nitride, LiN_3 [Li^+N^{3-}], which acts as a strong reducing agent.

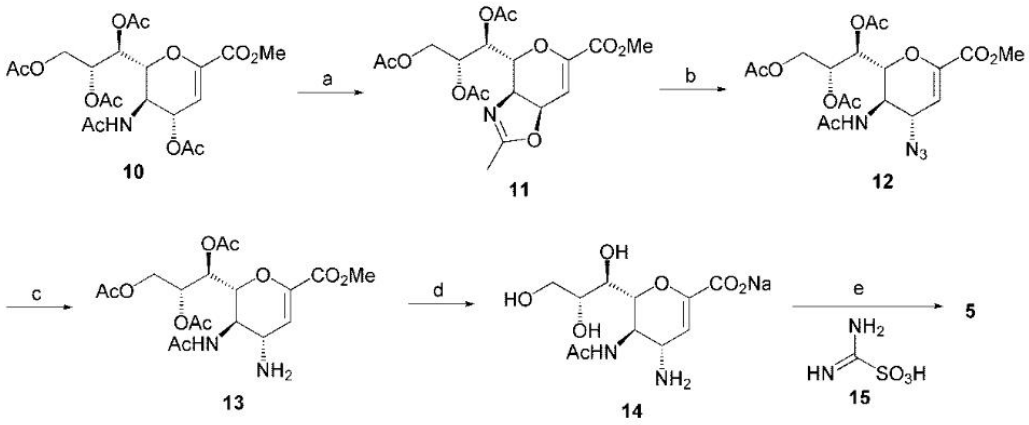


Figure 6.8 Monash synthesis of Tamiflu (Ac is an abbreviation for acetyl, $CH_3C{=}O$)

The first commercial scale production was developed by the pharmaceutical company Glaxo. (SK) They avoided the use of lithium nitride but still used azides (containing the unstable azide ion, N_3^-) and ion exchange chromatography as a purification technique rather than the greener recrystallization.

Activity 6.4
Draw three resonance structures for the azide ion, N_3^-.

Since then a number approaches to synthesizing Tamiflu have been developed, each with a more sustainable route. One of the problems is that one of the naturally occurring starting materials is a compound called shikimic acid which is currently uneconomical to synthesize and is isolated from the Chinese star anise plant (*Illicium anisatum),* a spice. One green approach is its production by fermentation via bioengineering *E.coli* bacteria.

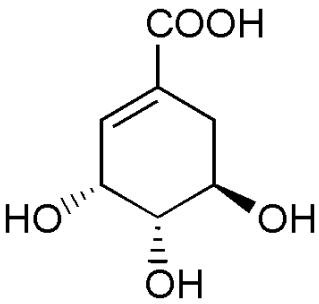


Figure 6.9 Shikimic acid (3,4,5-trihydroxycyclohex-1-ene-1-carboxylic acid)

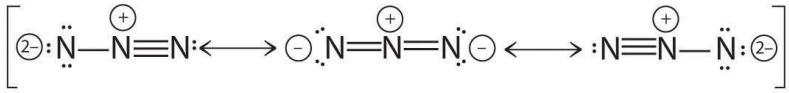
Activity 6.5
Deduce the molecular formula and identify three functional groups in the shikimic acid molecule. Add asterisks next to the chiral centres and deduce the number of stereoisomers (assuming no geometric isomerism).

Figure 6.10 Chinese star anise fruits and seeds

Activity 6.6

The raspberry flavoured ester 2-methylpropyl methanoate can be formed by reacting 2-methylpropan-1-ol with methanoic acid in the presence of an acid catalyst.
Write an equation for this reaction and calculate an approximate value for the atom economy. (A_r: O = 16, C = 12 and H =1).

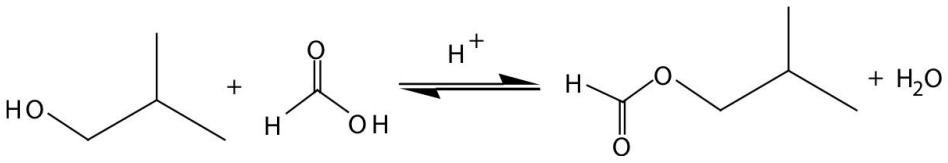
Activity 6.4 answer



Activity 6.5 answer

$C_7H_{10}O_5$; carboxylic acid, alcohol (hydroxyl) and alkene; three –OH groups, $2^3 = 8$

Activity 6.6 answer



M_r (alcohol) = 74.0: M_r (methanoic acid) = 46.0: M_r (ester) = 102: M_r (H_2O) = 18.0:

$$\% \text{ atom economy} = \frac{102.0}{(74.0 + 46.0)} \times 100\% = 85.0\%$$

The drawback of atom economy is that assumptions have to be made. For example, inorganic reagents (such as potassium carbonate in a synthesis of an ether (by the Williamson ether synthesis) are ignored as they are not incorporated into the final product. Also, solvents are ignored, as is the stoichiometry of the reagents.

The atom economy calculation is a very simple representation of the "greenness" of a reaction as it can be carried out without the need for experimental results. However, it is useful as a low atom economy at the design stage of a reaction prior to entering the laboratory can drive a cleaner synthetic strategy to be formulated.
Chemists have devised 'clever' catalysts called phase transfer catalysts, for example, organo-metallic substances, which bring the reactants together at the water-organic interface. Propene, hydrogen and carbon monoxide can be made to react with 95% selectivity by using a phase transfer catalyst containing a rhodium(I) complex. Rhodium (Rh) is a transition metal.

$$C_3H_6 + CO + H_2 \rightarrow H_3CCH_2CH_2CHO$$

Figure 6.13 Principles of green chemistry

Principles of green chemistry

1. Wastes Prevention
2. Atom Economy
3. Less Hazardous chemical synthesis
4. Design safer chemicals
5. Safer solvents and auxiliaries
6. Energy efficiency
7. Renewable feedstocks
8. Reduce derivatives
9. Catalysis
10. Design for degradation
11. Real time analysis for pollution preventions
12. Safety – accident prevention

D7. Paclitaxel (Taxol) – a chiral auxiliary case study

Understandings:

- Paclitaxel (Taxol) is a drug that is commonly used to treat several different forms of cancer.
- Paclitaxel (Taxol) naturally occurs in Pacific Yew trees but is now commonly synthetically produced.
- A chiral auxiliary is an optically active substance that is temporarily incorporated into an organic synthesis so that it can be carried out asymmetrically with the selective formation of a single enantiomer.

Applications and skills:

- Explanation of how Paclitaxel (Taxol) is obtained and used as a chemotherapeutic agent.
- Description of the use of chiral auxiliaries to form the desired enantiomer.
- Explanation of the use of a polarimeter to identify enantiomers.

A. Cancer Cells and Normal Cells

Cancerous tumors are characterized by cell division, which is no longer controlled as it is in normal tissue. Normal cells stop dividing when they come into contact with like cells while cancer cells no longer have the normal checks and balances in place that control and limit cell division.

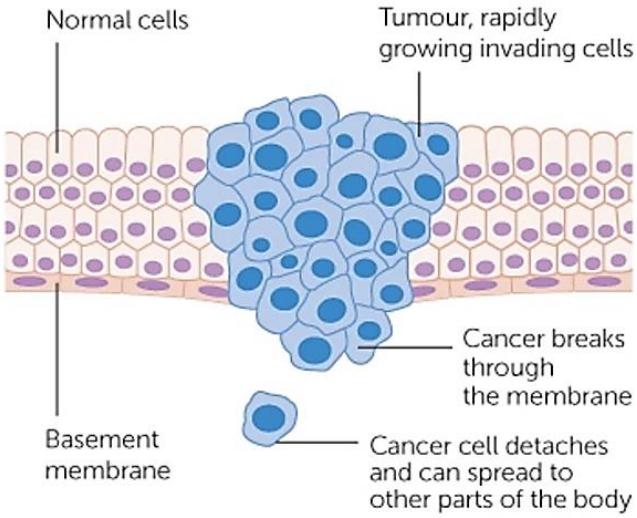


Figure 1: Cancer cells and normal cells

B. Paclitaxel (Taxol) – Anticancer drug

Paclitaxel (Taxol), an anticancer drug, is injected into the veins for the treatment of breast, ovarian, lung, bladder, prostate, melanoma, esophageal, as well as other types of solid tumor cancers. Paclitaxel (Taxol) and the semi-synthetic analogue docetaxel (as seen in Figure 1) are important anticancer agents.

Paclitaxel (Taxol) acts by preventing cell division – it does this by binding to microtubules in the cytoplasm, preventing them from breaking down during cell division as they block polymerization, hence stopping mitosis (Figure 2).

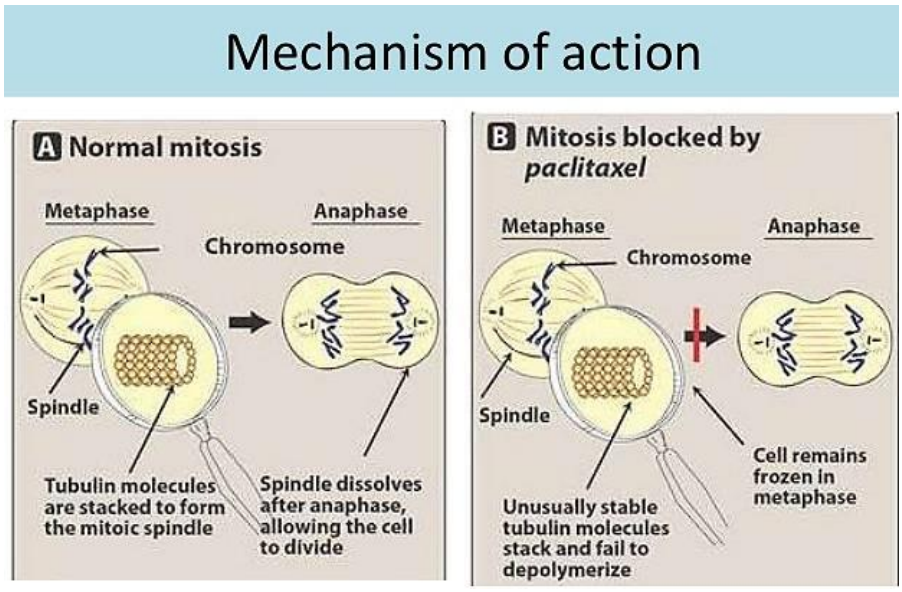


Figure 2: Mechanism of action of Paclitaxel (Taxol)

Common side effects of paclitaxel (Taxol) include: hair loss, muscle and joint pains, and diarrhea, among others.

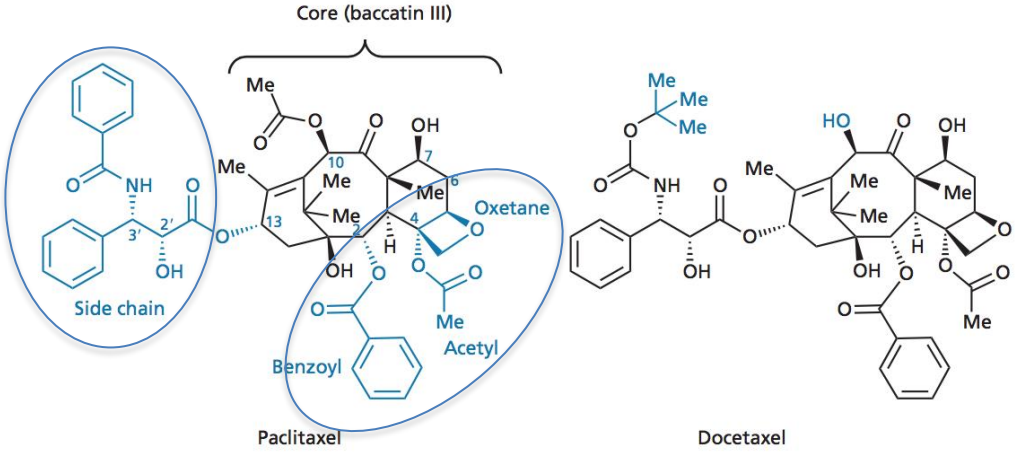
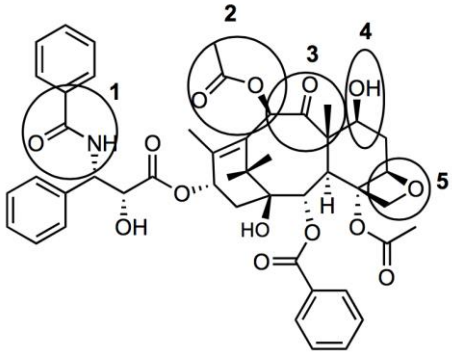


Figure 3: Paclitaxel (Taxol), with important binding groups in circle and docetaxel.

Activity

Identify and name the circled functional groups 1 to 5 in the structure of paclitaxel (Taxol) below.



C. Ways to obtain of Paclitaxel (Taxol)

1. Bark of the Pacific Yew trees
   Paclitaxel (Taxol) was isolated from the bark of Pacific Yew trees and identified in 1971 following a screening programme for new anticancer agents carried out by the US National Cancer Institute. Amounts of paclitaxel (Taxol) found in the bark are so tiny that it took over two tons of bark to yield just 10 grams of pure material. The Pacific Yew tree is also the world's slowest growing tree and obtaining paclitaxel (Taxol) from the bark will involve chopping the trees down. Advanced, expensive technology and complex purification techniques are also needed for such extractions.

Figure 4: The bark of the Pacific Yew Tree is peeled to provide Paclitaxel.

2. Full synthesis of paclitaxel (Taxol)
   A full synthesis of Paclitaxel (Taxol) can be carried out but such a move is impractical for large-scale production because it involves 30 chemical steps and gives a low yield. Overall, the low yield limit and the complexity of biosynthesis hampered its applicability.

3. Using 10-Deacetylbaccatin III obtained from European Yew trees
   It was feasible to isolate relatively large quantities of the compound 10-deacetylbaccatin from the leaves of the European Yew. A semisynthetic route is used to produce paclitaxel (Taxol) from 10-deacetylbaccatin III, which can be collected in adequate quantities from tree trimmings without damaging the trees themselves. 10-Deacetylbaccatin III is a precursor to the anti-cancer drug docetaxel (Brand name: Taxotere). Advanced, expensive technology and complex purification techniques are also needed for such extractions.

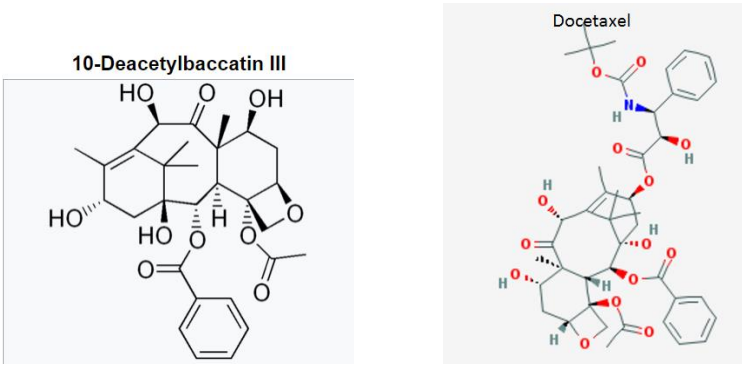


Figure 5: Structures of 10-deacetylbaccatin III and docetaxel (Taxotere).

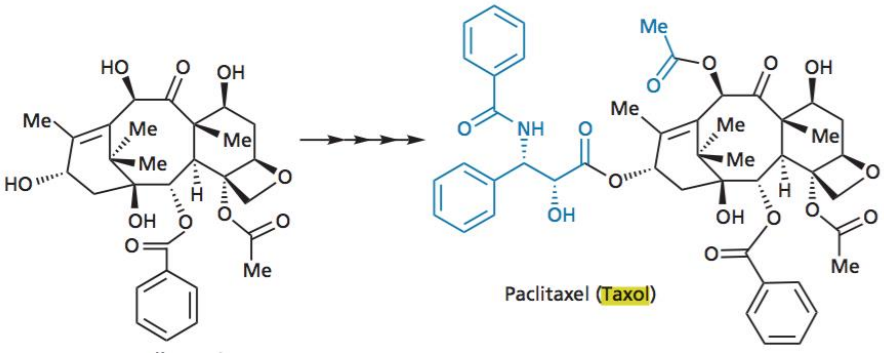


Figure 6: Semisynthesis of paclitaxel(Taxol) from 10-deacetylbaccatin III.

4. Fermentation
   Plant cell cultures represent an alternative, environmentally sustainable source of Paclitaxel (Taxol). Advantages of this method are growth of the material independent of its original location and not being subjected to seasonality or weather.

D. Optical Isomers

Paclitaxel contains 11 chiral centers as seen below:

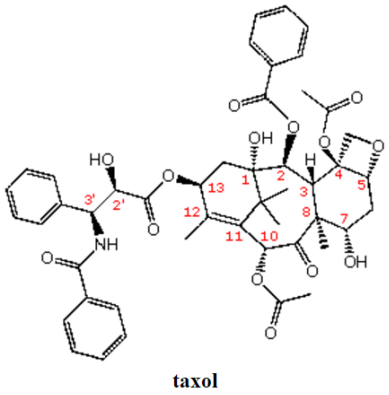


Figure 7: Chiral centers in paclitaxel

The chiral center is an atom connected to four different substituent groups. If there is one chiral atom in a molecule there will be two enantiomers. Enantiomers, are mirror image pairs that cannot be superimposed on each other. An example of a pair of enantiomers is provided by 2-butanol.

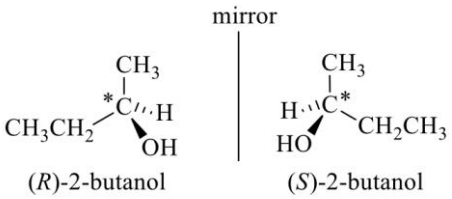


Figure 8: Enantiomers of butan-2-ol

Enantiomers have identical chemical properties except when interacting with other chiral molecules. They also have identical physical properties except when interacting with polarized light. The enantiomers of an optically active substance can be distinguished using a polarimeter because they rotate the plane of plane-polarized light in equal but opposite directions.

A simple polarimeter consists of a source of light, usually producing one specific wavelength, a sample tube and a scale to measure the degree of rotation of the plane polarized light

Figure 9: Polarimeter

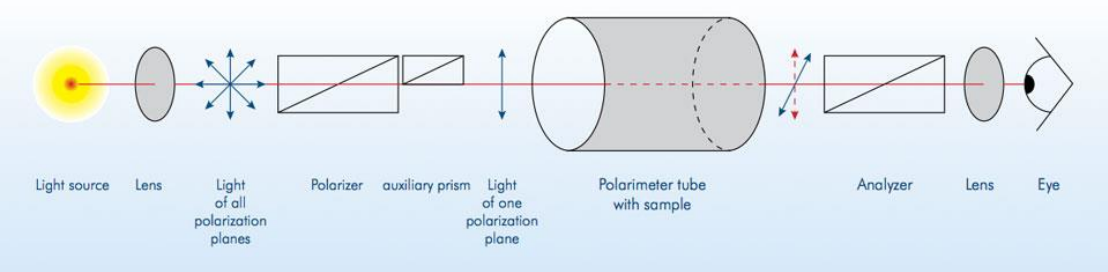


Figure 10: Rotation of plane polarized light by optical isomer

An enantiomer that rotates plane-polarized light to the right (dextrorotatory) is called the (+)-enantiomer and one that rotates the plane to the left (levorotatory) is called the (−)-enantiomer. For a 50:50 mixture of two enantiomers, the (+) rotation from one enantiomer will exactly equal the (–) rotation from the other enantiomer. Such mixtures are called racemic mixtures and they do not display optical activity.

E. Use of Chiral Auxiliary

Many drugs have chiral centers and so can exist as two enantiomers but it is usual for drugs and pharmaceutical companies to develop the enantiomer that has a therapeutic effect. Synthesis reactions normally produce a mixture of both enantiomers or racemic mixture which are difficult and expensive to separate.

Stereoselectivity refers to the preferential formation in a chemical reaction of one product stereoisomer (enantiomer or diastereomer) over another, as a result of inherent reaction specificity, or the influence of chiral features in the substrate, reagent, catalyst or environment.

One method of achieving stereoselective synthesis involves the use of a chiral auxiliary. As shown in Figure 11, this chiral auxiliary and combines with the non-chiral reactant to form a chiral intermediate. The presence of the chiral auxiliary will cause the reaction to follow a certain path that favors the production of one of the possible enantiomers. Once the reaction is complete, the chiral auxiliary is removed to form the desired drug. The chiral auxiliary are usually recycled for use in other reactions.

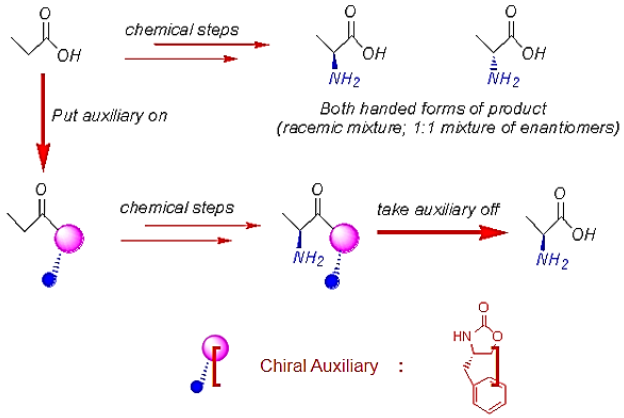


Figure 11: Synthesis of One Enantiomer using a Chiral Auxiliary

D8. Nuclear medicine

Understandings:

- Alpha, beta, gamma, proton, neutron and positron emissions are all used for medical treatment.
- Magnetic resonance imaging (MRI) is an application of NMR technology.
- Radiotherapy can be internal and/or external.
- Targeted alpha therapy (TAT) and Boron Neutron Capture Therapy (BNCT) are two methods which are used in cancer treatment.

Applications and skills:

- Explanation of why technetium-99m is the most common radioisotope used in nuclear medicine based on its half-life, emission type and chemistry.
- Explanation of why lutetium-177 and yttrium-90 are common isotopes used for radiotherapy based on the type of radiation emitted.
- Balancing nuclear equations involving alpha and beta particles.
- Calculation of the percentage and amount of radioactive material decayed and remaining after a certain period of time using the nuclear half-life equation.
- Discussion of common side effects from radiotherapy
- Explanation of TAT and how it might be used to treat diseases that have spread throughout the body.

A. Nuclear chemistry

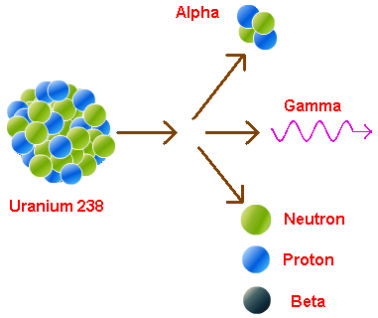
Overview

Nuclear chemistry deals with the study of nuclear particles, nuclear forces and nuclear reactions. The discovery of radioactivity by Henri Becquerel has spurred a great deal of research and further led to the discovery of artificial radioactivity. The release of huge amounts of energy through nuclear fission reactions became possible, not only in providing alternatives to fossil fuels, but also in providing radioisotopes for use in nuclear medicine.

NOS
The discovery of radioactivity is one of the significant discoveries stumbled upon by chance. Refer to page 906 of the Higher-Level Chemistry Textbook by Catrin Brown and Mike Ford to find out how Henri Becquerel discovered radioactivity.

Radionuclides

Radionuclides are generally heavy mass elements which are unstable due to the instability of the nucleus. They either undergo a spontaneous **decay** or nuclear reaction producing various types of **ionizing radiation** (Figure 1). The three most common types of radiation include alpha (α) particle, beta (β) particle, and gamma (γ) radiation. The decay process of atomic nuclei is also known as **radioactivity**.



Source of picture: https://nuclear-energy.net/definitions/radioactivity.html

Figure 1: Decay process of atomic nuclei

> **Note**!
> An unstable nucleus is referred to as a radioactive nuclide (or radionuclide).

Characteristics of Common Ionizing Radiation

The following table shows the characteristics of the three most common ionizing radiation produced by various radionuclides.

	Alpha ($^{4}_{2}\alpha$) particle	Beta ($^{0}_{-1}\beta$) particle	Gamma radiation
Characteristics	The ejection of a proton	The ejection of an electron from the conversion of a neutron to a proton	The release of energy with short electromagnetic wave ($\lambda < 10^{-13}$ m) & high frequency $>10^{19}$ Hz by the emission of photon
Common sources	Most heavy isotopes (Z > 83), e.g. ^{212}Pb, ^{225}Ac	Some heavy & most light radioisotopes, e.g. ^{90}Y, ^{131}I, ^{117} Lu, ^{192}Ir, ^{14}C	^{60}Co, ^{99m}Tc, ^{131}I, ^{137}Cs
Ionizing power	Very high approx. 100 × that of β particles	Low	Low
Penetrating power	Low; easily stopped by a piece of paper	can pass through paper but stopped by aluminium foil	Only stopped by concrete lead or heavy shielding

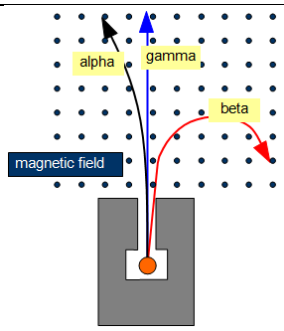
Action of magnetic field	 *Source of picture: http://www.schoolphysics.co.uk/age14-16/Nuclear%20physics/text/Magnetic_deflection_of_radiations/index.html*

Table 1: Characteristics of the most common ionizing radiation

Other ionizing radiations include:

- The ejection of a neutron
- The conversion of a proton to a neutron with the ejection of **positron**, an antiparticle of an electron with the same mass but positively charged.
  Since the positron is the anti-particle of the electron, the collision between matter and antimatter results in the emission of energy radiation as the two particles annihilate each other. This process is called annihilation.

The Use of Radionuclides in Medicine

The **ionizing power** (ionization effect) of a particle or radiation refers to the ability to cause ionization of the adjacent particles. Radioactivity is known as ionizing radiation as it results in ionization of an atom in contact and causes the removal of electrons. The exposure of living cells to emissions causes biological molecules to form radicals. The double helical structure of DNA can break when ionized, leading to cell death or mutations which triggers the onset of cancers. Hence, the exposure of radiative sources should be minimized where possible.

However, the ionizing effect of a particle is exploited as a useful tool for diagnosis and medical treatments. In general, a particle with high ionizing power produces more energy to a small region. Thus they are more destructive to the biological materials. This is the basis of a form of radiotherapy known as TAT.

Representing Decay Process with Nuclear Equations

The decay process usually produces a new radionuclide (**daughter nucleus**) that has a lower energy than its **parent nucleus**. The process can be represented by a nuclear equation. Note that the total number of nucleons (neutrons and protons) in a nuclear reaction is **conserved**, i.e. the mass number and the atomic number must equal on both sides of the equation (Table 2).

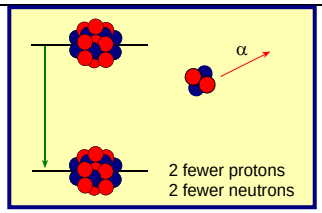
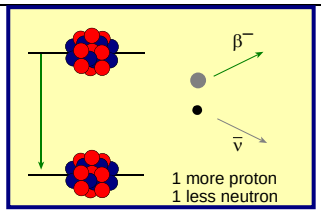
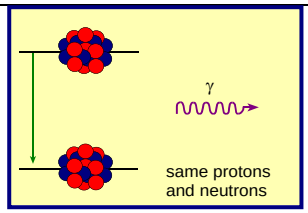
	Alpha ($^{4}_{2}\alpha$) particle	Beta ($^{0}_{-1}\beta$) particle	Gamma radiation
Nuclear equation	$^{238}_{92}U \rightarrow {}^{234}_{90}Th + {}^{4}_{2}\boldsymbol{\alpha}$ $^{226}_{88}Ra \rightarrow {}^{222}_{86}Rn + {}^{4}_{2}\boldsymbol{\alpha}$	$^{234}_{90}Th \rightarrow {}^{234}_{91}Pa + {}^{0}_{-1}\boldsymbol{\beta}$ $^{14}_{6}C \rightarrow {}^{14}_{7}N + {}^{0}_{-1}\boldsymbol{\beta}$	$^{238}_{92}U \rightarrow {}^{234}_{90}Th + {}^{4}_{2}\boldsymbol{\alpha + \gamma}$
Change in mass number	decrease by 4 units	no change	no change
Change in atomic number	decrease by 2 units	increase by 1 unit	no change
Graphic representation			

Table 2 Representing Decay Process with Nuclear Equations

Activity 1

1. Write balanced equations for the following nuclear reactions:

   (a) Americium-241 undergoes alpha decay:
   (b) Iodine-131 decays by beta (minus) emission:
   (c) An excited cobalt-60 nucleus emits gamma radiation and alpha particle

2. Complete the following nuclear equations. Indicate the symbol, the mass number, and the atomic number of the unknown particle. (c) is an example of electron capture.

   (a) $^{13}_{7}N \rightarrow {}^{13}_{6}C + \_\_\_\_\_$;
   (b) $^{11}_{6}C \rightarrow {}^{11}_{5}B + \_\_\_\_\_$;
   (c) $^{61}_{29}Cu + {}^{0}_{-1}\boldsymbol{\beta} \rightarrow \_\_\_\_\_$;

Determining Half-life of Radioactive Decay

Radioactive decay follows the first-order reaction.
Consider the decay process of radionuclide N, the rate expression for the decay can be expressed as rate = λ[N].

Integrated rate : $\ln \frac{N_t}{N_o} = -\lambda t$

$$N_t = N_o e^{-\lambda t}$$

where λ = decay constant

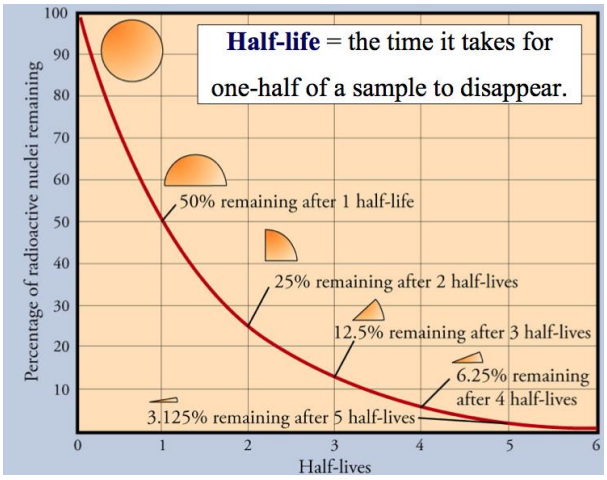
Since half-life of a first-order process is constant,

$$t_{1/2} = \frac{ln2}{\lambda} = \frac{0.693}{\lambda}$$

In other words, the half-life of a decay process is dependent on the decay constant, λ of the reaction.
Given that the initial amount of radionuclide undergoes a decay process (Figure 2),

$N_o \longrightarrow$ ½ $N_o \longrightarrow$ ¼ $N_o \longrightarrow \longrightarrow$ N_t

Number of half-life, *n* can be determined by the equation $\left(\frac{1}{2}\right)^{\frac{t}{t_{\frac{1}{2}}}} = \frac{N_t}{N_o}$



Recall that
The half-life of a reaction is the time taken for an initial amount of reactant to be halved.

Figure 2: Half-lives of a reaction

The shorter the half-life of a radionuclide, the higher the rate of decay is. Unlike most chemical reactions, the rate of natural radioactive decay is not influenced by external conditions, such as temperature and pressure.

Worked example

Given that the half-life of a radioactive substance is 6.8 hours, determine
(a) the duration taken for a 20.0 kg sample to decompose to 12.6 kg,
(b) the decay constant of the reaction

(a) $\left(\frac{1}{2}\right)^{\frac{t}{t_{\frac{1}{2}}}} = \frac{N_t}{N_o}$

$\left(\frac{1}{2}\right)^{\frac{t}{6.8}} = \frac{12.6}{20.0}$ $\left(\frac{t}{6.8}\right) \ln\frac{1}{2} = \ln\frac{12.6}{20.0}$

$t = \ln\frac{12.6}{20.0} / \ln\frac{1}{2} \times 6.8$

$= 4.5327$

$\approx$ 4.5 hours (2 s.f.)

(b) $t_{1/2} = \frac{ln2}{\lambda}$

$\lambda = \frac{0.693}{t_{1/2}}$

$= \frac{0.693}{6.8}$

$= 0.1019$

$\approx 0.10\ hr^{-1}$ (2 s.f.)

Worked example

The half-life of carbon-14 is approximately 5730 years. Using this data and the growth decay formula, $N_t = N_o e^{-\lambda t}$, determine the decay constant, λ, for carbon-14.

$N_t = N_o e^{-\lambda t}$

$\frac{N_t}{N_o} = 0.5$, $\lambda = -\ln\frac{0.5}{t_{1/2}}$

$\lambda = -\ln\frac{0.5}{5730}$

$= 1.21 \times 10^{-4}$ years^{-1}

Worked Example

4.80 mol of $^{128}_{53}\mathrm{I}$ undergoes a beta decay to form $^{128}_{52}\mathrm{Te}$. Given that the half-life of $^{128}_{53}\mathrm{I}$ is 2.50 min, calculate the percentage of $^{128}_{53}\mathrm{I}$ that decayed when the radionuclide is allowed to decay for 20.00 minutes. Subsequently, determine the amount of $^{128}_{52}\mathrm{Te}$ formed.

$\frac{t}{t_{1/2}} = \frac{20}{25}$

$= 0.8$

$N_t = N_o\left(\frac{1}{2}\right)^{\frac{t}{t_{\frac{1}{2}}}}$

$N_t = (0.5)^{0.8}$

$= 0.5743$ (4 s.f.)

Amount of $^{128}_{53}\mathrm{I} = 4.80 \times 0.5743$

$= 2.7569$ mol (4.s.f.)

% $^{128}_{53}\mathrm{I}$ decayed $= (1 - \frac{2.7569}{4.8}) \times 100$

$= 42.57$

≈ 42.6 % (3 s.f.)

The nuclear equation representing the beta decay of $^{128}_{53}\mathrm{I}$ is

$$^{128}_{53}\mathrm{I} \rightarrow {}^{128}_{52}\mathrm{Te} + {}^{0}_{-1}\beta$$

Since 2.7569 mol of $^{128}_{53}\mathrm{I}$ is remaining,
amount of $^{128}_{52}\mathrm{Te}$ formed $= 4.80 - 2.7569$

$= 2.0431$

≈ 2.04 mol (3.s.f)

Problems

1. A certain isotope has a half-life of 6.00 hours. How much of a 5.00 g sample will be left after 24 hours?

2. Carbon-14 has a half-life of 5730 years. How long will it take for a 1.00 kg sample to be reduced to 0.25 kg of carbon-14?

3. An isotope with a half-life of 8 hours was received exactly 24 hours before it was to be used. At the time of use, the quantity of the isotope was 16.5 g. How much of the isotope was there upon delivery to the lab?

B. Medical Applications of Nuclear Chemistry

Nuclear medicine refers to the use of radiation in medical practice in two major areas: nuclear imaging and radiotherapy. The applications can be depicted in the following flow chart (Figure 3).

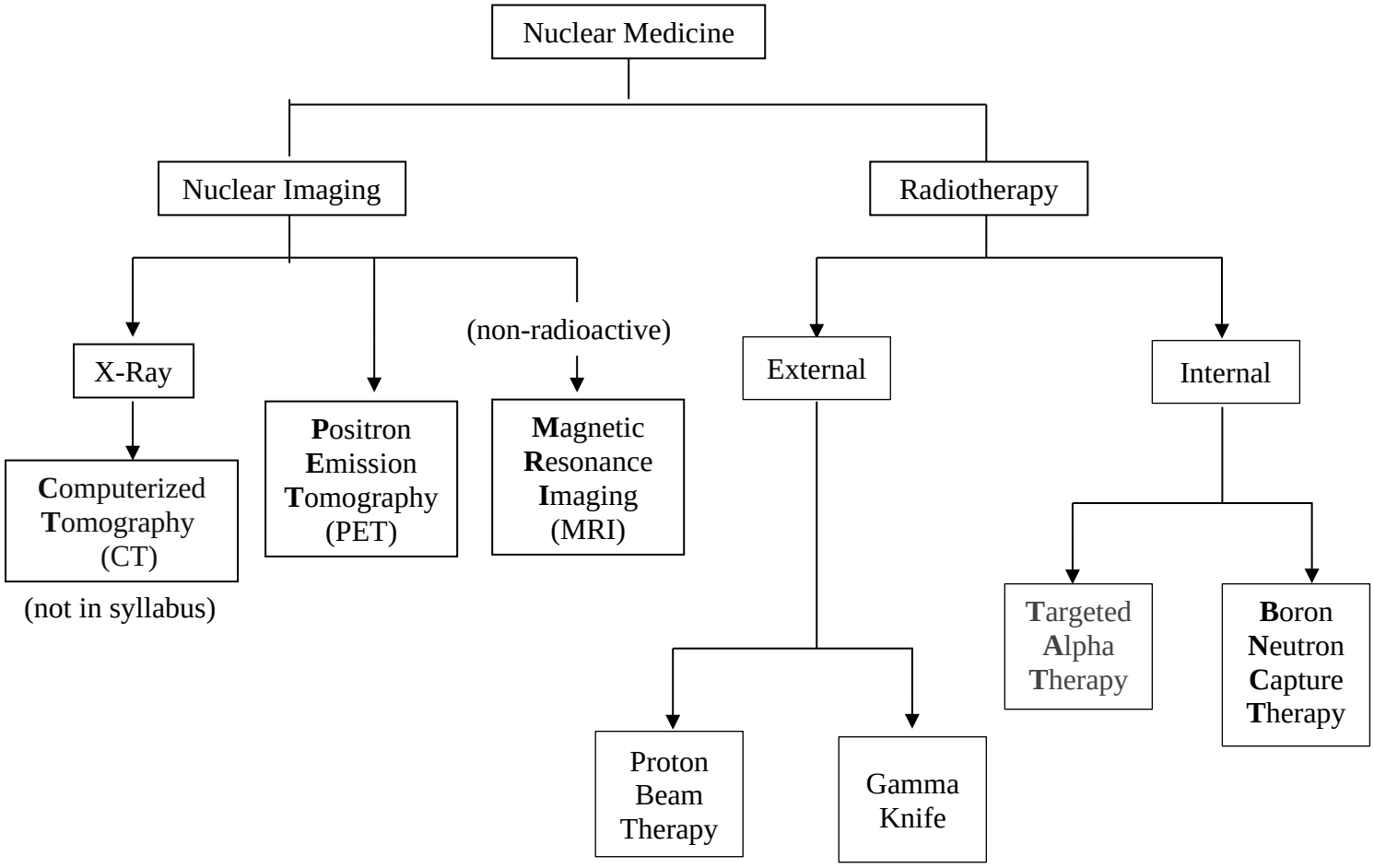


Figure 3 Overview of the application of nuclear medicine

Radiotherapy (See Section D) can be performed externally or internally. Radionuclides used for external radiotherapy are ideally be alpha or beta emitters to ensure high ionizing radiation that sufficiently kill the targeted cells outside human body. On the other hand, an internal radiotherapy involves the introduction of radionuclides in small amount into the patient's body by injection, swallowing, or inhalation. The radionuclide is often chemically bonded to a biologically active substance where it is designed to go to a specific place in the body where there could be disease or an abnormality, as shown in Figure 4.

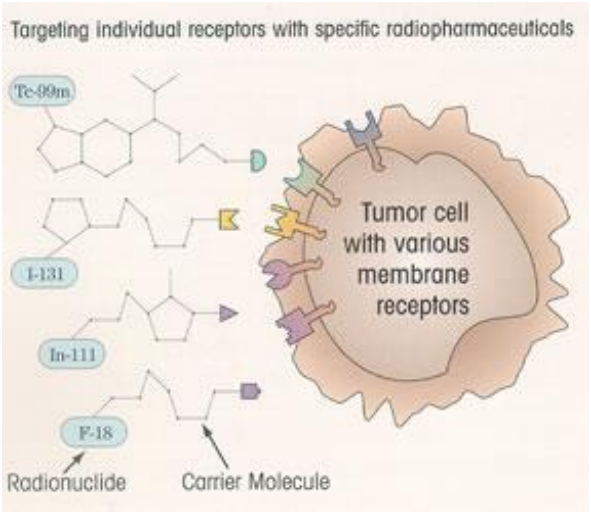


Figure 4 Targeted delivery of radionuclide to the tumor cell

Radionuclides used for internal radiotherapy are commonly alpha or beta emitters that also emit gamma rays to enable imaging.

Incorporation of radionuclides in cells or in the body also allows *radiolabeling* (also known as tagging or tracer studies) to follow a particular type of molecule in its pathway through an organism, or serves as a diagnostic tool to visualize targeted body tissues. It does not directly change the normal sequence of chemical events that occurs as low doses of radioisotopes are used. This technique is also commonly known as **nuclear imaging** (refer Section C). Radionuclides used solely for diagnostic purpose should ideally be gamma emitters, as alpha radiation is easily absorbed and would cause unnecessary exposure to highly ionizing radiation.

In order to safely use radionuclides in medicine, not only must the dose be well controlled, but the half-life of the isotope must be relatively short so that the radioactivity is quickly reduced, causing no long-term problems. Technetium-99m, for example, is one of the most common radionuclides used as it has a relatively short half-life (approx. 6h). It also binds with many biological molecules which allows it to be easily localized onto targeted tissue. In addition, it emits gamma radiation which facilitates detection for diagnosis.

Note
It is important to understand that chemistry and radioactivity are completely independent processes. The use of radionuclides in biological studies and in medicine is completely based on the nuclear properties of the radionuclide while a chemical reaction is based on valence electron interactions and does not depend at all on nuclear properties.

Common Isotopes Used for Radiotherapy

Some commonly used radionuclides are listed in Table 2.

Radioisotope	*Half-Life*	*Radiation*	*Applications*
Technetium-99m	*6 h	γ	Most widely used
Iodine-123	13 h	γ	SPECT brain imaging
Carbon-11	20 min	e^+	PET
Iodine-131	*8.1 days	β,γ	Thyroid disorders
Phosphorus-32	*14 days	β	Large variety of uses in biology and medicine
Thallium-201	74 h	γ	Heart imaging
Gallium-67	78 h	γ	Tumor imaging
Chromium-51	*28 days	γ	Red blood cell survival

*Produced in nuclear reactors; otherwise produced in an accelerator.

Table 2 Commonly used radionuclides in medicine

Technetium(Tc)-99m

Technetium(Tc)-99m is the most common radionuclide used and can be combined with many different molecules to act as a *radiopharmaceutical* as it has the following advantages (Table 3).

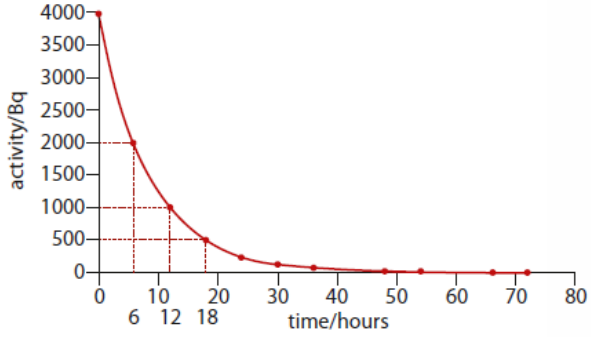
a half-life of 6 hours	 Radiodecay of Technetium-99m Half-life of 6 hours allows Tc-99m to remain in the body for sufficiently high activity to be examined by scanning but also decays quickly enough to minimize exposure to the patient
produces gamma rays and low-energy electrons and does not emit β-particles	Low dose of radiation as high-energy β-particles are not emitted. Low-energy gamma rays escape easily and can be accurately detected
chemically versatile	It can be bound to a range of biologically active substances, which serves as a good tracer

Table 3 Features of Tc-99m as a radionuclide for medical applications

Technetium-99m (Tc-99m) is an artificial element generated from the decay of molybdenum-99 (half-life of about 66 h).

$$^{99}_{42}\mathrm{Mo} \rightarrow {}^{99m}_{43}\mathrm{Tc} + {}^{0}_{-1}\beta$$

It is commonly extracted on site for hospital studies using a radionuclide generator. **Radionuclide generator** is a widely used method to produce certain short-lived radionuclides in a hospital or clinic **to minimize the need for transportation** so the use of the radionuclides can be fully optimized before decay takes place. It involves obtaining a relatively long-lived radionuclide which decays into the short-lived nuclide of interest.

Tc-99m is an excited state known as **metastable state**. A nucleus in an excited state may reach its ground or unexcited state by the emission of a gamma ray. Hence it loses its excess energy emitting a gamma-ray to become Tc-99m. The reaction can be expressed as:

$$^{99m}_{43}\mathrm{Tc} \rightarrow {}^{99}_{43}\mathrm{Tc} + \gamma$$

Lutetium-177

Lutetium-177 is a radionuclide with a half-life of 6.7 days and is a beta/gamma emitter. Since lutetium-177 produces highly ionizing beta particle and gamma radiation, it is often used in conjunction with a peptide (small protein) to selectively target neuro-endocrine tumors.

Yttrium-90

Yttrium-90 is another highly ionizing radiation producer (a beta emitter) with a half-life of 2.67 days. Yttrium-90 therapy is often used in the treatment of liver cancer. Large numbers of small plastic or glass beads containing yttrium-90 are injected directly into the arteries that supply blood to the liver.

Lead-212

Lead-212 is an alpha emitter with a half-life of 10.6 hours. Lead-212 has shown promising results in treating a variety of cancers by binding with highly specific antibodies.

C. Nuclear Imaging

Nuclear imaging is widely used in the diagnosis of the abnormal lesions deep in the body without exploratory surgery. The visualization of the targeted area is done when the gamma rays produced by the radionuclides is detected by a gamma camera to create images of the inside of patient body for evaluation. With this feature, the function of internal organs such as kidneys and stomach can be assessed.

Nuclear imaging is also used to trace cancers and to evaluate the efficacy of treatment of a disease. In addition, radionuclides also act as a tracer which travels through the area and emits gamma rays. Its travelled path can be used as an assessment for functionality. For example, the function of heart can be evaluated for coronary artery disease. Nuclear medicine procedures can be used to evaluate the damage to the heart after a heart attack.

Gamma camera

A gamma camera uses tracers, e.g. Tc-99, to produce images (Figure 5). The radionuclide is attached to a biologically active molecule that will be taken up by the tissue to be studied. Once the radionuclide has been absorbed by the body the gamma rays are directed towards a crystal (usually sodium iodide with a small amount of thallium added) through a lead collimator, which consists of a lead circle which has a regular number of holes drilled in it. This absorbs all the gamma rays that enter the collimator at an angle. The gamma photons that pass straight through the collimator hit the crystal and cause it to scintillate. The gamma ray excites electrons in the crystal causing them to give off visible light. This light is detected by a bank of photomultiplier tubes which build up an image of the levels of gamma radiation being emitted from different parts of the tissue.

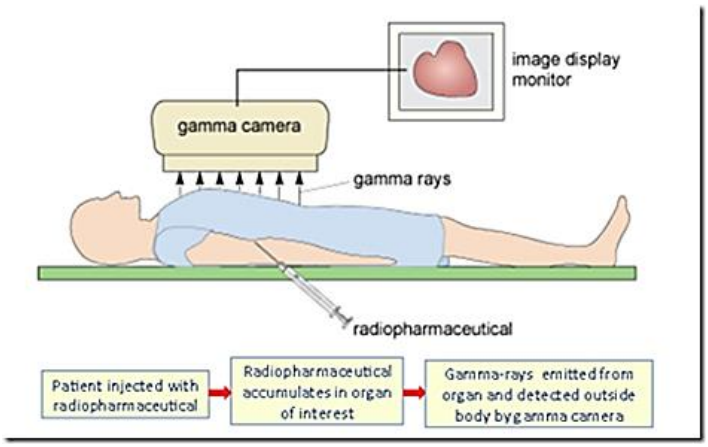


Figure 5 Nuclear imaging using gamma camera

Positron Emission Tomography (PET)

Positron **E**mission **T**omography, **PET** is a well-established scanning technique used in medical applications, particularly for clinical doctors and researchers to measure in detail the functioning of distinct areas of the human brain while the patient is comfortable, conscious and alert. The technique is largely used as an investigative tool for studies of the chemical process involved in the working of healthy or diseased human brains.

PET represents a new step forward in the way scientists and doctors evaluate brain functions as it is able to produce images of the brain at work while an X-ray or a CT scan shows only structural details within the brain.

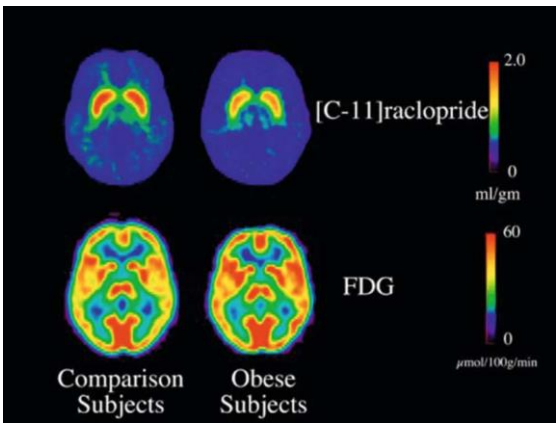


Figure 6

PET scan of brain showing the effects of Ritalin (methylphenidate, a drug prescribed for millions of young people with attention deficit hyperactivity disorder (ADHD)) on the number of dopamine transporters available (red more, blue less).

PET scanner works by detecting the gamma rays produced by the annihilation (collision between matter and anti-matter) of a positron (anti-electron) and an electron. The positrons are released during the decay of the nuclei of specific radioisotopes, such as fluorine-18 (Figure 7). The information is then fed into a computer to be converted into a complex picture of the patient's working brain.

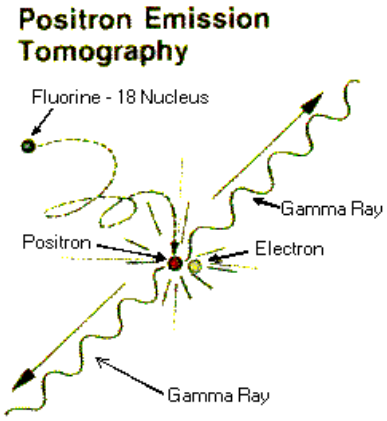
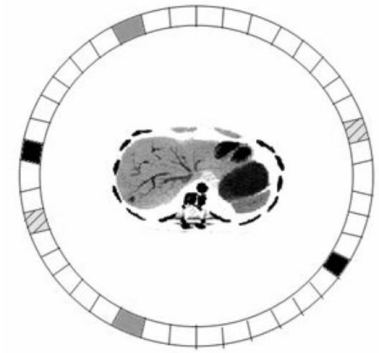


Figure 7 Gamma ray production

Activity

1) A cross section of a PET scanner is shown below. The detectors shaded in show gamma rays which were detected at the same time.



By drawing lines between the pairs of detectors that detected gamma rays, can you draw where you think the tumour is?

2) What does PET stand for?
3) What type of radiation do the isotopes used in PET scans emit?
4) What happens when this particle meets an electron?
5) What is then produced?
6) What is the name of the machine used to produce the isotopes?

Magnetic Resonance Imaging [MRI]

Some elements have odd mass number, e.g. hydrogen, have an intrinsic property called nuclear spins. This makes them behave like small magnets. MRI make uses the spin property of odd nucleons to produce an electromagnetic radiation for diagnosis. The principle of signal generation is the same as that of nuclear magnetic resonance (NMR).

During the analysis, an external applied magnetic field causes the proton nuclei in patient's body to align themselves, in almost equal numbers, either with the field lines (in parallel) or exactly opposite to the field (antiparallel). As radio waves are directed at the hydrogen nuclei at the same frequency, they will flip from one alignment to another so producing a magnetic field. The nuclei will revert back to their original state giving off electromagnetic radiation when the radio wave is turned off. The signal then detected by the scanner. Figure 8 illustrates the process of electromagnetic radiation emission.

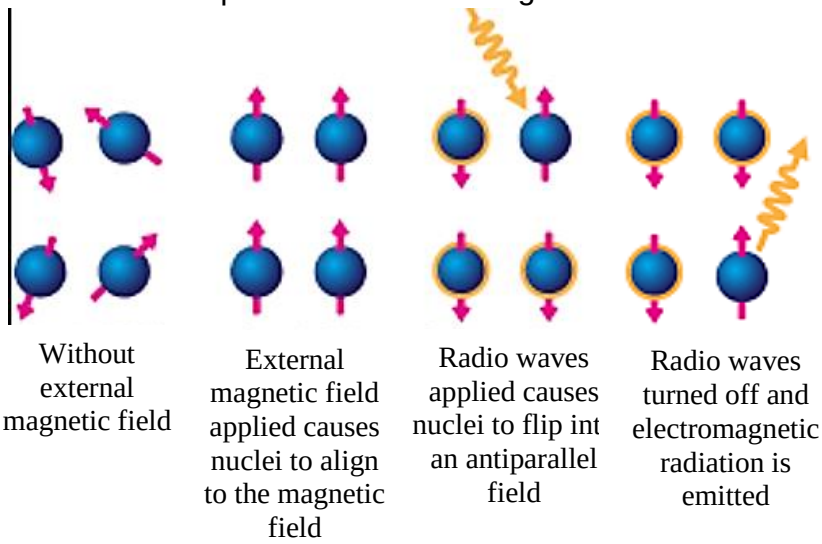


Figure 8 Principles of electromagnetic radiation

The time taken for the nuclei to return to their original state is called the **relaxation time**, and depends on what tissue type the nuclei are in. By measuring the various properties of the MRI signal along with the relaxation time a detailed image of a cross section of the body can be built up.

Magnetic resonance imaging is particularly good in obtaining high quality images of soft tissue such as the brain, but is not as good for harder objects such as bone.

Some comparison between MRI and other imaging techniques, including X-rays, PET and ultrasound can be summarized by the following table:

Technique	MRI	Ultrasound, X-rays and PET
Advantages	Non-invasive No known side effects High quality images of soft tissue. Image can be made for any part/orientation of the body	Ultrasound is non-invasive, cheap, and not known to have side effects X-ray produces clear images of bones and metals PET provides good resolution in biochemical and metabolic functions for disease detection
Disadvantages	. Images of hard tissue such as bone are poor. Uncomfortable for the patient, causes claustrophobia. Very expensive.	Ultrasound produces relatively poor image resolution – interpretation subject to experience of the medical practitioner X-rays and PET High radiation dose for the patient. People working with X-rays need to take care to limit their annual dosage.

Table 4 Advantages and disadvantages for various nuclear imaging options

D. Radiotherapy

Radiotherapy is one of the first line treatment options for cancers alongside surgery and chemotherapy by the fact that the cancerous cells are rapidly dividing and particularly sensitive to damage by radiation. The ionizing effect of the radionuclide is primarily affecting DNA that controls the cell division and hence can prevent their division.

Cancer arises when normal cells lose their regulatory mechanism for cell growth and division, eventually divide rapidly to form a lump of abnormal cells known as **tumor**.

However, the radioisotopes also attack healthy cells that divides rapidly, although the damage is to a lesser extent due to their rate of cell division. This is major consideration in the administration of radiotherapy.

External radiotherapy

External radioethepy procedures is carried out by having an external source of radiation is directed at the site of cancer in the body from a radioactive source, commonly cobalt-60 which have a half-life of 5.26 years. Co-60 undergoes a beta decay to produce nickel-60 and emits gamma rays.

$$^{60}_{27}\mathrm{Co} \rightarrow {}^{60}_{28}\mathrm{Ni} + {}^{0}_{-1}\beta + \gamma\text{-rays}$$

Modern radiotherapy includes the use of linear accelerators (linacs for short) which produce very high energy X-ray beams directed at the tumor as well as the use of gamma knife radiosurgery. The gamma knife has cobalt-60 sources positioned to precisely target the radiation.

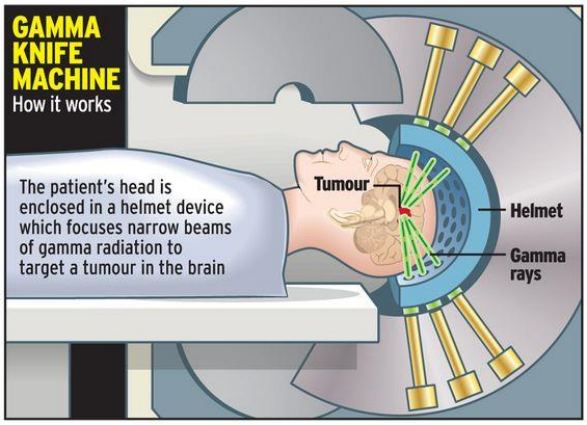


Figure 9 Gamma knife machine

The treatment is planned using CT or MRI images, so that the sources are correctly targeted to irradiate the tumor and avoid healthy tissue, especially around the eye and cochlea.

Both techniques give the advantage of greater precision in targeting at the tumor with minimum damage to the surrounding tissues, which is essential for the case of tumor located in vital organs such as brain.

Internal radiotherapy

Internal radioethepy procedures is carried out by introducing a radioisotope, either orally or injection as a liquid; or in solid form as implant.

One major concern with radiotherapy and most standard chemotherapy drugs is the selectivity as the drugs work by killing any cells that grow and divide rapidly in the body, which can sometimes lead to serious side effects. This triggers the development of targeted therapy which work by selectively target on certain parts of cancer cells that make them different from other cells. Cancer cells are typically different from normal cells as due to changes in their genes (DNA). These gene changes might cause the cell to make too much of a certain protein, which in turn promote rapid cell growth and division. **Hence, the radioisotopes can be introduced to these cancer cells by binding itself to an antibody that recognizes the protein expressed by cancer cells**.

One known example is **targeted alpha therapy, TAT**. TAT uses an alpha-emitting radioisotope bound to an antibody which direct them to the target cancer cell. Alpha particles are able to kill the cancer cells as they have very high ionizing radiation yet are short range that the irradiation of normal tissue surrounding the targeted cells are minimized. To date, TAT has shown promising results for the treatment of pancreatic, ovarian and melanoma cancers using lead-212.

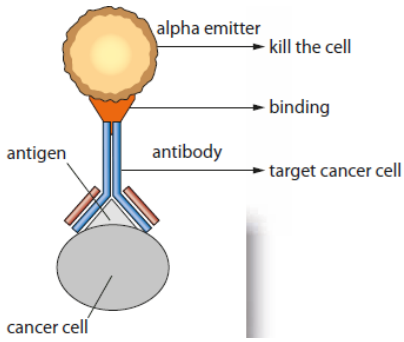


Figure 9 Binding of an antibody tagged with a radioisotope onto the cancer cell

Boron neutron capture therapy (BNCT)

High intensity boron neutron beams are used in boron neutron capture therapy, which uses the ability of stable boron-10 nuclei to absorb neutrons. A high dose of non-radioactive boron-10 isotope is administered to the patient by intravenous injection, which eventually accumulates in high concentration at the cancerous site. A subsequent irradiation of neutron with low energy allows absorption of neutron by boron-10 nuclei and then transmuted into an unstable boron-11 nucleus, which immediately undergoes alpha decay:

$$^{10}_{5}\mathrm{B} + ^{1}_{0}n \rightarrow {}^{11}_{5}\mathrm{B} \rightarrow {}^{7}_{3}\mathrm{Li} + {}^{4}_{2}\mathrm{He}$$

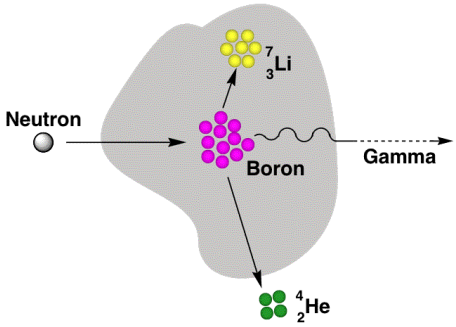


Figure 10 Boron neutron capture therapy

Boron neutron capture therapy can be used to treat cancers which are normally treated with radiotherapy, such as lymphomas and skin cancers, as well as cancers of the brain, breast, lung, head and neck, bone, prostate, pancreas and cervix. In addition, when surgical removal of a tumor is planned, BNCT may also be used to help reduce the size of the tumor and to reduce the associated normal tissue loss. Boron neutron capture therapy is less demanding for the patient than conventional radiotherapy as it can be given several times over a period of 2-4 days while in contrast conventional radiotherapy needs to be given up to 30 times over a period of six weeks. In addition, non-radioactive isotopes are introduced to the patient.

Proton beam therapy

Proton beam therapy (Figure 11) or proton therapy is a recent development of nuclear medicine that irradiates cancerous tissues using protons. A linear accelerator is used to impart high kinetic energies to protons in a narrow beam directed at a tumor. The protons damage the cell DNA, ultimately causing them to die or be unable to divide. Cancer cells are particularly vulnerable to DNA damage because of their high rate of cell division.

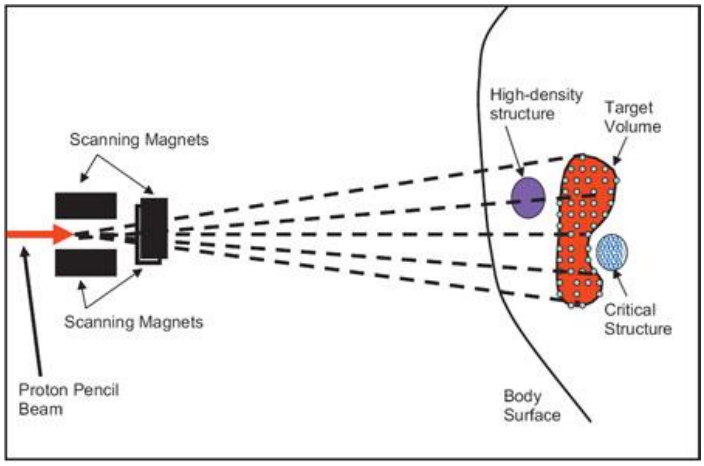


Figure 11 Proton beam therapy

In contrast to other types of nuclear or ionizing radiation, the protons reach a maximum absorption within a narrow range, deep inside the patient's body. This allows the proton beam to be focused on the tumor with minimal damage to surrounding healthy tissue. To treat tumors at greater depths, the proton accelerator must produce a beam of protons with higher kinetic energy. Tumors closer to the surface of the body are treated with protons with lower kinetic energy.

E. The Effects of Radiation

All three types of ionizing radiation disrupt normal cellular processes in living organisms. The biological effect of radiation depends on the type of cells exposed to radiation, the radiation dose, and the duration of radiation. A person exposed to ionizing radiation may suffer either short or long-term injury, depending on the radiation dose received. Cancer is often the main delayed effect of ionizing radiation.

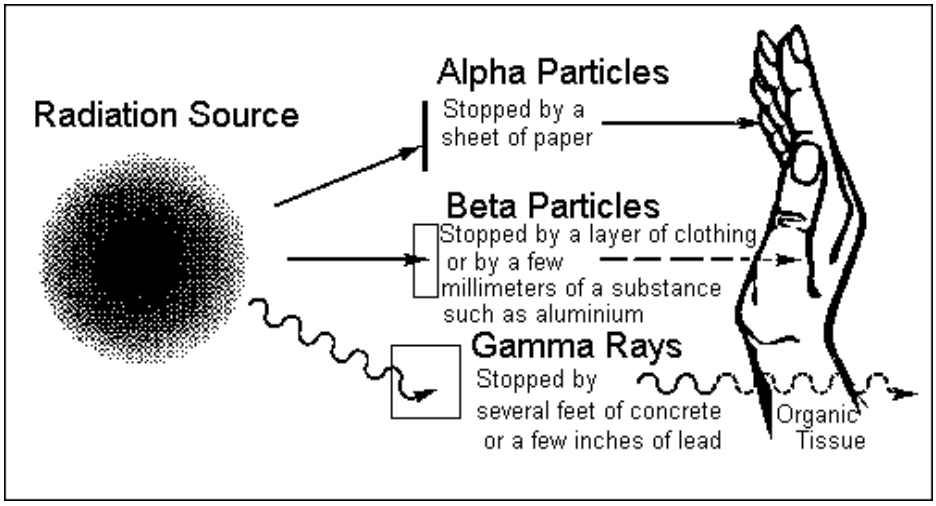


Figure 11 Effects of Radiation

The chemical properties of radioactive substances are also important factors in biological effects of radiation. The damage from internal radiation source depends on how long the radioactive substance stays in the body. For example, strontium-90 (a radioisotope) is particularly dangerous because of its similar chemical properties to calcium, it tends to accumulate in the bone where it may cause leukemia and bone cancer.

In general, more side effects are presented in external radiotherapy than internal therapy. The extent of side-effects varies greatly amongst individuals, but the following common side-effects are observed:

- Fatigue
- Nausea
- Hair-loss
- Sterility
- Skin reaction

Summary

- Nuclear chemistry deals with the study of nuclear particles, nuclear forces and nuclear reactions.
- Three types of nuclear radiation exist known as alpha, beta, and gamma radiation.
    - Alpha radiation is the ejection of ${}^{4}_{2}\alpha$ nuclei
    - Beta emission involves the ejection of an electron from the conversion of a neutron to a proton
    - Gamma emission is the release of energy with short electromagnetic wave and high frequency by the emission of photons.
- Radioactivity is represented in nuclear equations, where the totals of the mass numbers and atomic numbers on both sides are equal.
- Radioactive decay is governed by an exponential decay of the numbers of radioactive nuclei N, $N_t = N_o e^{-kt}$, where N_o is the number of such nuclei at time zero and $\boldsymbol{\lambda}$ is the decay rate for the process. The half-life of the reaction is the time for half of the nuclei to decay and is related to the decay rate by $t_{1/2} = \frac{ln2}{k} = \frac{0.693}{k}$.
- Number of half-life, n can be determined by the equation $\left(\frac{1}{2}\right)^{\frac{t}{t_{\frac{1}{2}}}} = \frac{N_t}{N_o}$.
- Nuclear medicine is used for diagnostic of body function, or as therapeutic procedures in which the radiation is used to treat disease, usually cancer. It consists of a radionuclide and the radiation emitted may be detected from outside the body by a radionuclide imaging device, for example, a gamma camera or be detected in a body fluid, e.g., urine or blood plasma.
- Radionuclides used as nuclear medicine must deliver the minimum possible radiation dose to the patient. Radionuclides used in radiotherapy are ideally an alpha or beta emitters which produce high ionizing radiation dose to the diseased organ or tumor while minimizing the radiation dose to non-target issues. A low abundance gamma photon is an advantage, allowing the activity distribution to be imaged. It should have a fairly short half-life, typically several days is preferable.
- The radionuclide for nuclear imaging should ideally be gamma emitters with relatively short half-life. It should not emit charged particles as these are absorbed within a few millimeters of tissue.

Worked half-life problems - Answer

1. $\left(\frac{1}{2}\right)^{\frac{t}{t_{\frac{1}{2}}}} = \frac{N_t}{N_o}$.

   $(\frac{1}{2})^{\frac{24}{6}} = \frac{x}{5}$

   x = (5.00 g)(1/2)$^{4.00}$
   = (5.00 g)(1/16)
   = 0.3125 g
   ≈ 0.313 g

2. (0.25 kg) / (1.00 kg) = 0.25 = (1/2)^n
   n = 2; 2.0 = T/ 5,730 years
   T= (2.0)(5,730 years) = 11, 460 years = 11,000 years

3. 24 hours / 8 hours = 3 = n
   $\frac{16.5\text{ g}}{x}$ = (1/2)^3
   m_i = (16.5 g) / (1/8) = 132 g

Activity answers

Activity 1

1. (a) $^{241}_{95}Am \rightarrow {}^{238}_{93}Np + {}^{4}_{2}\alpha$
   (b) $^{131}_{53}I \rightarrow {}^{131}_{54}Xe + {}^{0}_{-1}\beta$
   (c) $^{60}_{27}Co \rightarrow {}^{56}_{25}Mn + {}^{4}_{2}\alpha + \gamma$

2. (a) $^{13}_{7}\text{N} \rightarrow {}^{13}_{6}\text{C} + {}^{0}_{1}\beta$
   (b) $^{11}_{6}\text{C} \rightarrow {}^{11}_{5}\text{B} + {}^{0}_{1}\beta$
   (c) $^{61}_{29}\text{Cu} + {}^{0}_{-1}\beta \rightarrow {}^{61}_{28}Ni$

Activity 2

PET- Answers

2) Positron emission tomography
3) Beta-+, positrons, positive electrons
4) They annihilate
5) Two gamma rays, travelling in opposite directions
6) A cyclotron
7) C-11, O-15, F-18
8) A)a cyclotron **b) PET scanner** c) gamma knife
9) tumour

D9. Drug Detection and Analysis

Understandings:

- Organic structures can be analyzed and identified through the use of infrared spectroscopy, mass spectroscopy and proton NMR.
- The presence of alcohol in a sample of breath can be detected through the use of either a redox reaction or a fuel cell type of breathalyzer.

Applications and skills:

- Interpretation of a variety of analytical spectra to determine an organic structure including infrared spectroscopy, mass spectroscopy and proton NMR.
- Description of the process of extraction and purification of an organic product. Consider the use of fractional distillation, Raoult's law, the properties on which extractions are based and explaining the relationship between organic structure and solubility.
- Description of the process of steroid detection in sport utilizing chromatography and mass spectroscopy.
- Explanation of how alcohol can be detected with the use of a breathalyzer.

Drug Detection and analysis

1. Introduction

With advancements in technology, the accuracy and sensitivity of drug analysis has improved. Modern analytical techniques are capable of detecting and analyzing minute amounts of illegal substances in the body, distinguish between stereoisomers of biologically active compounds, and confirm the identity and purity of pharmaceuticals. This improvements in technology helps safeguard society from substance abuse as well as improve one's quality of life.

Numerous analytical techniques are used for drug analysis and detection. These techniques include chromatography, nuclear magnetic resonance (NMR) and infrared (IR) spectroscopy (topics 11.3 and 21.1), mass spectrometry (MS) and X-ray crystallography (topic 21.1). Before analysis, isolation and purification processes have to occur using crystallization, distillation, or extraction techniques.

1.1. Drug Detection

1.1.1 Mass Spectrometer Detection

The abuse of performance-enhancement substances like steroids in sports is a significant problem worldwide. The most frequent substance used are anabolic steroids, which accelerate protein synthesis and cellular growth. They are prohibited by most sporting associations due to medical and ethical reasons.

Steroids and their metabolites can be identified using gas chromatography (GC) and mass spectrometry (MS). Most often, the method used for steroid detection in blood and urine is known as gas chromatography-mass spectrometry, GC-MS where the two techniques are combined in succession. Gas chromatography isolates the chemicals in the samples and the mass spectrophotometer performs identification and quantification of the components.

Being non-polar, anabolic steroids can be extracted from biological samples with organic solvents, then be concentrated for further study. These isolated steroid samples can be analyzed using MS to visualize their mass spectrum, which can be compared to collections of identified compounds.

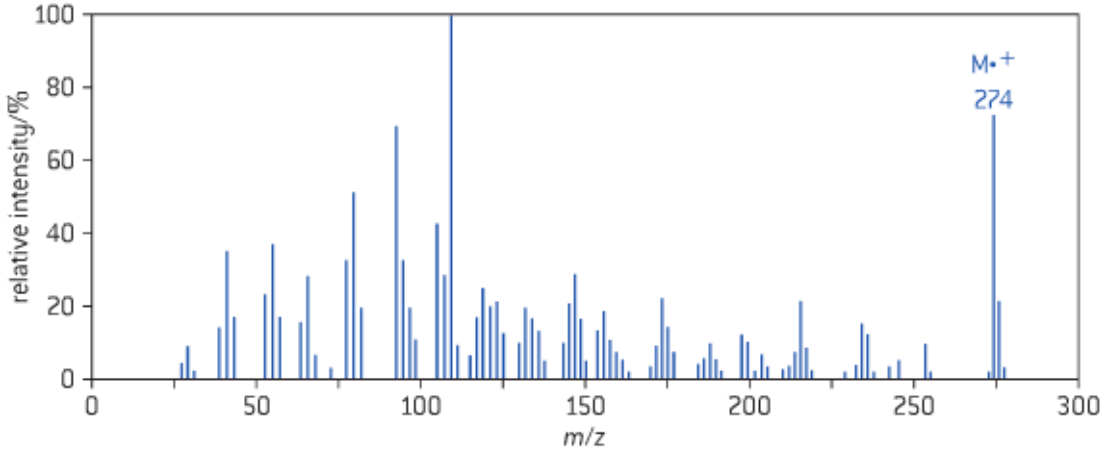


Figure 1: Mass spectrum of the anabolic steroid nandrolone (M_r = 274).

Quick tips to interpreting a mass spectrum

- The largest m/z usually corresponds to the molecular mass (denoted as M+) of the compound
- Fragments of the compound can be deduced based on the mass difference or the peaks of the lower masses

1.1.2 Gas Liquid Chromatography Detection

Gas liquid chromatography is used for the separation of and identification of volatile and thermally stable components in a mixture. The basic principle is that these constituents have varying affinities for two phases, a stationary phase and a mobile phase.

In gas liquid chromatography, the phases are:

- Stationary phase – a microscopic layer of a non-volatile *liquid*, usually a polymer, which coats the walls of a solid, non-reactive support structure (Figure 2)

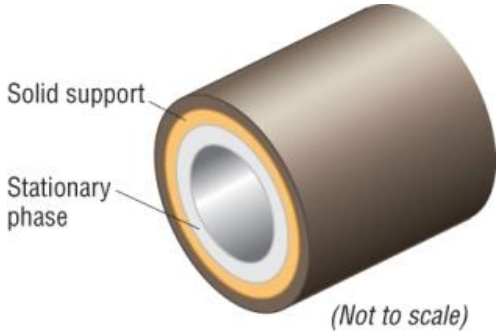


Figure 2: Cross section of a Gas Liquid Chromatography column

- Mobile phase – an inert carrier gas, such as argon or nitrogen, that acts as a transport medium by mixing with the vaporized sample

The constituents thus partition themselves between the gas and liquid phases. The samples can then be separated as they are carried across the liquid stationary phase by the mobile gases, based on their differences in affinities for the 2 phases as well as their molecular mass. The constituents of the mixture can be separated by the rate which they each move through the column and their boiling points. Molecules that are more volatile move through the column faster, whereas molecules with greater affinity towards the liquid phase will exit the column slower.

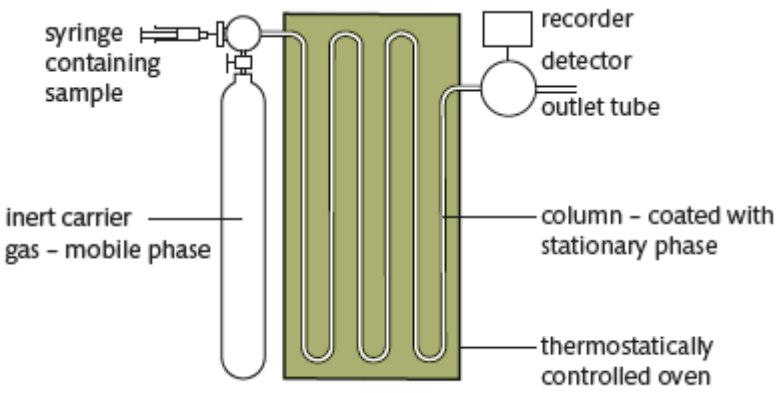


Figure 3: Gas chromatography setup

As mentioned earlier, depending on the nature of the partitioning between the gas and liquid phases, each constituent of the mixture will be eluted at a specific time interval known as its **retention time**. The eluted sample will pass to the mass spectrometer for detection through fragmentation patterns.

The passage of each constituent is recorded as a peak on the chromatograph. The area under the peak shows the concentration in comparison to a standard. An example of a simple gas chromatograph is given in Figure 4. The retention time for component X on the graph, t_R, is measured from the time of the injection of the sample to the detection of compound X.

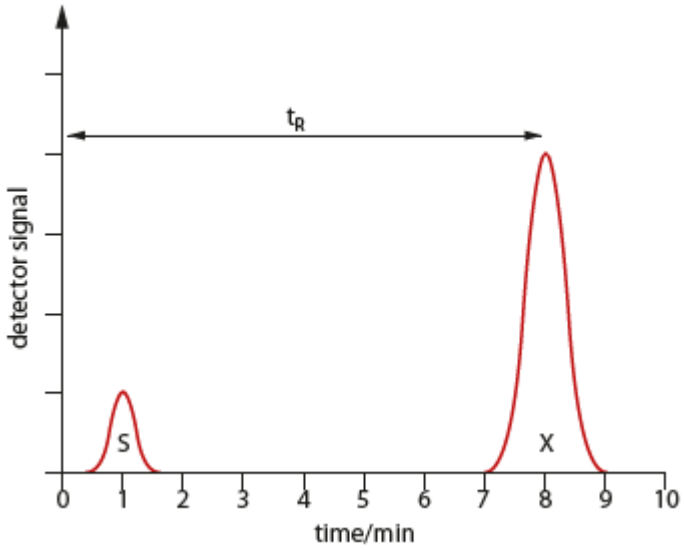


Figure 4: Sample of gas chromatogram

1.1.3 Breathalyzers Detection

Alcohol (ethanol) is the substance that is abused the most often globally. Overconsumption impairs judgement, concentration, and motor skills leading to violent behavior and road accidents. In most countries, a legal limit for the **blood alcohol concentration** (BAC) is in place for drivers or heavy machinery operators. Estimation of the BAC can be conducted using **breathalyzers**, allowing for the detection of alcohol concentration in the breath, which is approximately corresponds to the BAC.

Ethanol is a volatile compound, hence an equilibrium between blood and gas is achieved in the lungs. The gaseous ethanol in the lungs is then exhaled:

$$\underset{\text{in blood}}{C_2H_5OH(aq)} \rightleftharpoons \underset{\text{in exhaled breath}}{C_2H_5OH(g)}$$

There are two main types of commonly used breathalyzers – utilizing the oxidation of potassium dichromate(VI) or utilizing a fuel cell (fuel cell intoximeter).

a) Dichromate breathalyzer

The simplest breathalyzer comprises a glass tube filled with acidified solution of potassium dichromate(VI). When alcohol enters the tube, the orange solution turns green, as reduction of dichromate(VI) ions to chromium(III) ions occurs:

$$\underset{\text{orange}}{Cr_2O_7^{2-}(aq)} \rightarrow \underset{\text{green}}{2Cr^{3+}(aq) + 7H_2O(l)}$$

Depending on conditions, ethanol in the breathalyzer can be oxidized to ethanol or ethanoic acid.

$$\underset{\text{ethanol}}{CH_3CH_2OH} \rightarrow \underset{\text{ethanal}}{CH_3CHO + 2H^+ + 2e^-}$$

$$\underset{\text{ethanal}}{CH_3CHO + H_2O} \rightarrow \underset{\text{ethanoic acid}}{CH_3COOH + 2H^+ + 2e^-}$$

b) Fuel Cell Intoximeter

Another type of breathalyzer is known as the fuel cell intoximeter, and comprises a fuel cell.

The chemical reaction that takes place in an alcohol fuel cell converts ethanol to ethanolic acid. In the process, this conversion produces a fixed number free electrons per molecule of alcohol and H^+ ions are freed in the process and they combine with atmospheric oxygen to form water.

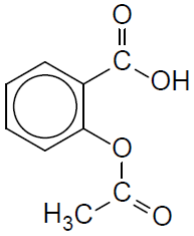
$$O_2(g) + 4H^+(aq) + 4e^- \rightarrow 2H_2O(l)$$
$$2H^+(aq) + \tfrac{1}{2}\,O_2(g) + 2e^- \rightarrow H_2O(l)$$

The upper surface of the intoximeter has an excess of electrons, and the lower surface has a corresponding deficiency of electrons. Hence, current flows through this external circuit to neutralize the charge. This current is a direct indication of the amount of alcohol consumed by the fuel cell. The fuel cell produces a linear relationship between current created and alcohol concentration in the breath sample. Fuel cell breathalyzers are widely used because of their accuracy and portability.

1.2. Drug analyzing

1.2.1 Spectroscopic analysis of drugs

Numerous drugs for pharmaceutical purposes are simple organic molecules with varying functional groups. These functional groups can then be analyzed and identified through IR, NMR, and mass spectroscopy. NMR spectroscopy being a primary ratio method of measurement is highly suitable to evaluate the quality of drugs. NMR spectroscopy can be used for the identification of a drug substance, the identification and quantification of impurities arising from the synthesis pathway and degradation, or residual solvents as well as the determination of the content in the assay.



aspirin

Figure 5: Aspirin structure

A ^{1}H NMR spectrum is generated as protons in different chemical environments produce signals with specific chemical shifts and splitting patterns. The characteristic NMR absorptions of aspirin's functional groups in the NMR spectrum are displayed in Figure 6. In Table *1*1, the analysis of the aspirin's ^{1}H NMR spectrum provides more information about its structure.

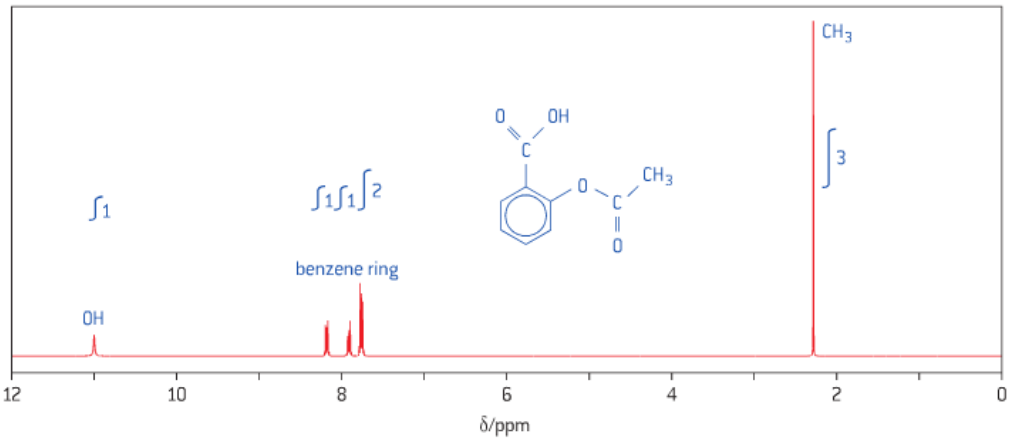


Figure 6: ^{1}H NMR spectrum of aspirin

Chemical environment	Chemical shift / ppm	Number of protons (integration)	Number of adjacent protons	Splitting pattern
CH_3	2.3	3	0	none (singlet)
C_6H_4 (benzene ring)	7.7, 7.9, and 8.2	4 (2 + 1 + 1)	—	multiplets*
OH	11.0	1	0	none (singlet)

Table 1: Aspirin's chemical shifts and splitting patterns of protons (splitting pattern of protons in the benzene ring is not assessed)

Besides NMR, infrared spectroscopy (IR can be used for the elucidation of the molecular structure by identifying the functional groups present in aspirin.

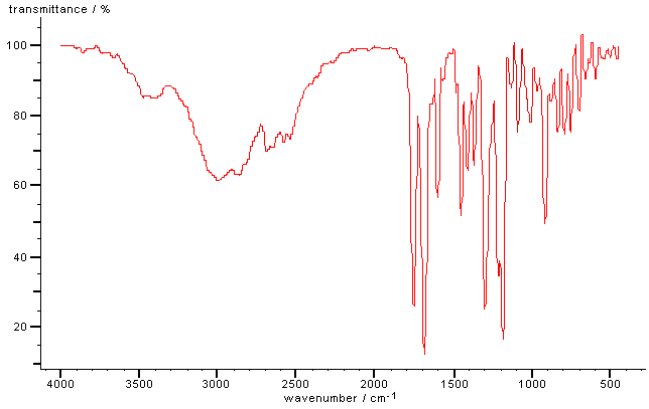


Figure 7: IR Spectrum of aspirin

Bond / (Functional group)	Absorption / cm^{-1}
O-H	2900 v. broad
C=O	1750
	1700
C-O	1200

Table 2: Analysis of IR spectrum of Aspirin

Aspirin's structure can be further confirmed by information obtained from its mass spectrum (Figure 8). As fragmentation occurs predictably, structural fragments such as CH^+ (*m/z* = 15) can be directly seen in the spectrum. The cation with *m/z* = 163 is formed by losing a hydroxyl radical (M_r = 17) from the molecular ion M^+ (*m/z* = 180). Additional species such as *m/z* = 92, 120, and 138 are formed through further fragmentation and rearrangement of the cations.

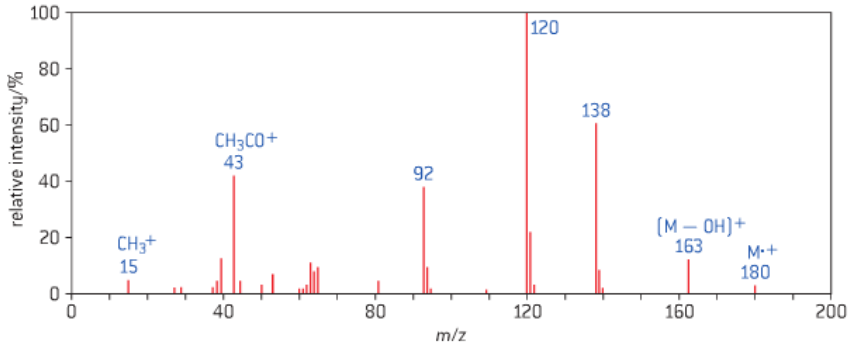


Figure 8: Mass spectrum of aspirin

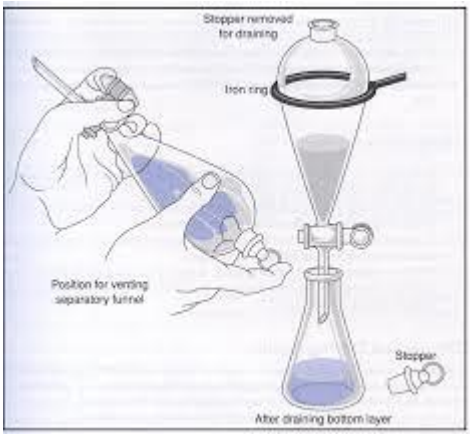
Thus, identities of lead compounds in drugs can be confirmed through the use of analytical techniques such as IR and ^{1}H NMR spectroscopy, and analysis of MS fragmentation patterns.

1.3 Process of extraction and purification

Synthesis of drug often requires separating the drug from the other impurities and by-products. Separation must be performed to obtain a pure product although it is often time consuming. Separation utilizes techniques that make use of the difference in physical properties to separate the components of in a mixture. Separation can be achieved by processes like solvent extraction, chromatography and fractional distillation.

a) Solvent Extraction

As learned in Chemical Bonding, solubility of solutes in its solvent depends on their abilities to interact and form bonds with the solvent molecules. Solvent extraction is a method to separate compounds based on their relative solubility in two different immiscible liquids, usually water and an organic solvent. It involves transferring of the solute dissolved in its original solvent to another immiscible liquid solvent.



As you shake the separating funnel it's normal for a gas to build up. Be Sure to Vent the Separating Funnel! You do this by spinning the stopcock to let a little air out. Failure to do this is a safety hazard; the cap would burst off your separating funnel.

Figure 9: Correct technique to use a separating funnel

Most organic compounds are much more soluble in organic solvents (ether, dichloromethane, etc.) than they are in water. This is because of the “like dissolves like” rule. Likewise, most salts are much more soluble in water than they are in organic solvents. Non-polar organic solvents, such as benzene, allow non-polar organic molecules to dissolve well, by forming London (dispersion) forces between the solute and solvent molecules. Often, these organic molecules are non-polar due to a high hydrocarbon content, including long carbon chains and aromatic rings, with a small proportion of polar functional groups.

Conversely, organic compounds that are soluble in polar solvents are polar in nature, with a larger proportion of functional groups. The molecules can dissolve by forming dipole-dipole interaction with the polar solvent molecules or H-bonds with polar protic solvents. Ionic salts are soluble in water by forming ion-dipole interactions with water molecules.

By mixing partially organic soluble samples in organic solvent (toluene, benzene, xylene), the organic soluble compounds will dissolve into the solvent and can be separated using a separating funnel. When allowed to dissolve in both, the solute is **unequally distributed** between the solvents. This distribution is known as a **partition** (Figure 10).

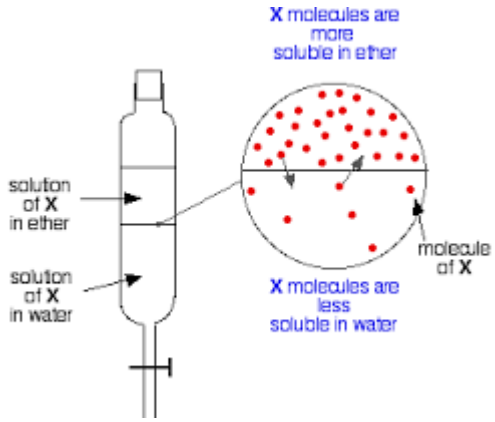


Figure 10: Illustration of partition of a solute in a separating funnel

The partition of a solute between two immiscible liquids is a form of heterogeneous equilibrium. For example, when iodine, I_2, is partitioned between an organic solvent and water, an equilibrium is formed:

$$I_2(aq) \rightleftharpoons I_2(org)$$

The equilibrium constant is known as the **distribution coefficient**, K_D, for organic : water system.

$$K_D = \frac{[I_2(org)]}{[I_2(aq)]} = \frac{\text{concentration of solute in organic layer}}{\text{concentration of solute in aqueous layer}}$$

Since partition is a process at equilibrium, the value of **distribution coefficient**, K_D, is dependent on the mixture's temperature. The partition coefficient of a system also depends on the polarities of the solute and solvent.

For example, the **distribution coefficient**, K_D, of iodine in ethoxyethane/water is 760 as iodine is more soluble in organic solvent than in water. On the other hand, the distribution coefficients of polar compounds in ethoxyethane/water are typically less than 1 as they are more soluble in polar solvents.

Calculation example:

1. A solute has a K_D between chloroform and water of 5.00. Suppose we extract a 50.00 cm^3 sample of a 0.050 mol dm^{-3} aqueous solution of solute with 15.00 cm^3 of chloroform.
    a. Determine the fraction of solute remaining in the aqueous phase after extraction.

        No of mole of solute 0.05 x 0.05 = 0.0025 mol
        Let no of mole extracted into chloroform be y mol.
        K_D = 5.00 = [y/0.015] / [0.0025-y/0.05]

        $5.00 = \frac{0.05y}{0.015\ (0.0025-y)}$

        0.0001875 – 0.075y = 0.05 y
        0.125y = 0.0001875
        y = 0.0015

        Fraction remaining = (0.0025- 0.0015)/0.0025 = 0.4 or 2/5

    b. Determine the volume of chloroform needed to extract 50 % of the solute.

        No of mole of solute 0.05 x 0.05 = 0.0025 mol

No of mole of solute in each phase = 0.0025 / 2 = 0.00125 mol

Let volume of chloroform be x dm^3

K_D = 5.00 = [0.00125/x] / [0.00125/ 0.05]
0.125 = 0.00125/x
x= 0.01 dm^3

b) Difference in volatility

For an organic compound to change from a liquid to gaseous state, must be overcome for the molecules to be separated. The boiling point is hence dependent on the strength of these forces: the stronger the intermolecular forces, the higher the boiling point, resulting in lower volatility. The factors that influence the strength of intermolecular forces in organic compounds are as summarized:

Molecular Size	Larger molecule size decreases volatility due to greater London (dispersion) forces
Polarity	Polar molecules have higher boiling points and decrease volatility due to their ability to form H-bonds or dipole-dipole interactions.

Differences in volatility can be used to separate **miscible** liquids mixture, bringing about the separation technique of **fractional distillation**. It makes use of the same principle as simple distillation – in mixture, liquids with lower boiling points will be distilled first. Fractional distillation differs in that better separation is achieved through the use of a **fractional column**, producing **fractions** as the product. This technique is applied in the separation of chemical feed-stock, such as phenols and toluene, as well as isolating liquid drug products from miscible liquid mixtures.

The theory of factional distillation is based on the relationship known as **Raoult's law**. The law states that the vapor pressure of a volatile substance A is proportional to the mole fraction of A in the mixture:

$$P_A = P^{\ominus}_A \times \chi_A \quad \text{----------} \quad \text{eqn (1)}$$

where

- P_A is the vapor pressure of substance **A** in the mixture (also known as the partial pressure) at a given temperature
- $P^{\ominus}_A$ is the vapor pressure of **pure** substance **A** at the same temperature

- χ_A is the mole fraction of substance **A**, which is the ratio of the number of moles of substance **A** to the sum of the total number of moles of all the components in the mixture.

$$X_A = \frac{\text{number of moles of A}}{\text{total number of moles in mixture}}$$

$P^{\ominus}_A$, the vapor pressure of **<u>pure</u>** substance **A**, is the pressure exerted by a vapor in an equilibrium with its liquid state, at a given temperature in a closed system.

$$\text{liquid} \underset{\text{condense}}{\overset{\text{boil / evaporate}}{\rightleftharpoons}} \text{vapour}$$

If the equilibrium tends further to the right, the volatility of the substance increases, thus, more molecules are present in the gaseous state to exert pressure on the liquid's surface i.e. greater vapor pressure. A liquid with lower boiling point (weaker intermolecular forces) will have a higher vapor pressure.

Note that Raoult's law only applies to **ideal solutions**. Similar to ideal gases, ideal solutions are assumed to be fully miscible as a solution. This operates on the assumption of identical intermolecular forces – in which the molecules in the solution behave similarly as to when the molecules are in a pure solution.

Raoult's law can be summarized in the graph shown below. For a mixture of solutions containing A and B, where component B has a higher vapor pressure than component A, according to Dalton's law, the total vapor pressure is the sum of the component vapor pressures for any composition of the mixture (eqn 2) .

$$P_T = P_A + P_B \quad \text{----------} \quad \text{eqn (2)}$$

Combining Dalton's law of partial pressures and Raoult's law to a mixture of ideal liquids A and B, the vapor pressure of the mixture is:

$$P_T = (P^{\ominus}_A \times \chi_A) + (P^{\ominus}_B \times \chi_B) \quad \text{----------} \quad \text{eqn (3)}$$

For a mixture containing only two components, A and B, the mole fraction is:

$$X_A = \frac{\text{number of moles of A}}{\text{number of moles of A} + \text{number of moles of B}}$$

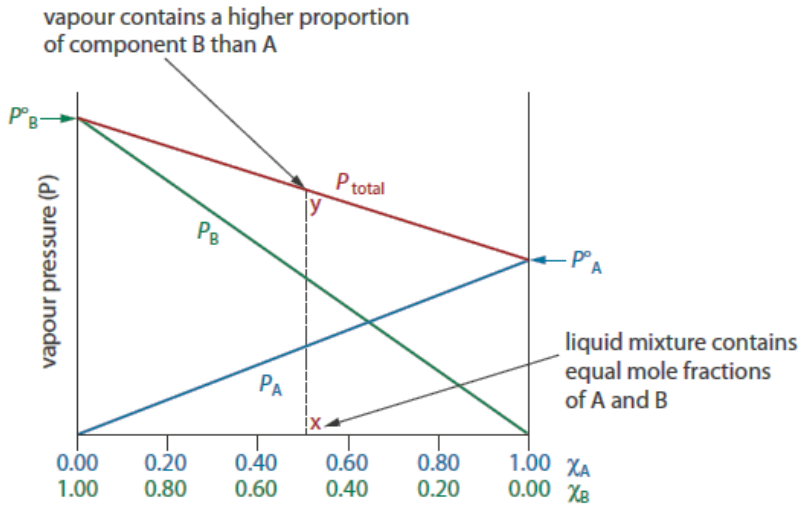


Figure 11: Binary liquid mixture

The application of Raoult's law is used to explain how fractional distillation is able to separate components in a miscible liquid mixture. When the mixture is boiled, the component with greater volatility (lower boiling point) will have greater vapor pressures, and will evaporate the fastest. This results in the vapor produced being richer with the more volatile components. Condensing the vapor will thus produce a condensate with a larger fraction of the more volatile component, in comparison to the original mixture as seen in Figure 12.

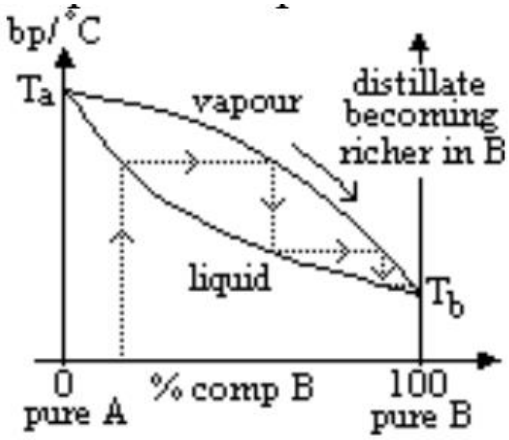


Figure 12: Heating and cooling results in separation

Fractional distillation uses the apparatus illustrated in Figure 13. The surface area inside the column is enhanced using glass beads or projections. Otherwise, an extremely long distillation column is required. As the solution boils, the vapor rises, cools, then condenses and trickles back down the wall of the column. The condensate is reheated by hot vapor rising, and evaporates, forming more vapor.

This process repeats in a cycle, allowing the vapor that rises to become enriched with the more volatile compound. This increases the mole fraction of the more volatile component, therefore increasing partial pressure of the volatile compound. The more volatile components rise up the column, and less volatile compounds remain lower in the column. Eventually, the vapor that escapes the column can be collected and condensed is enriched in the more volatile compounds.

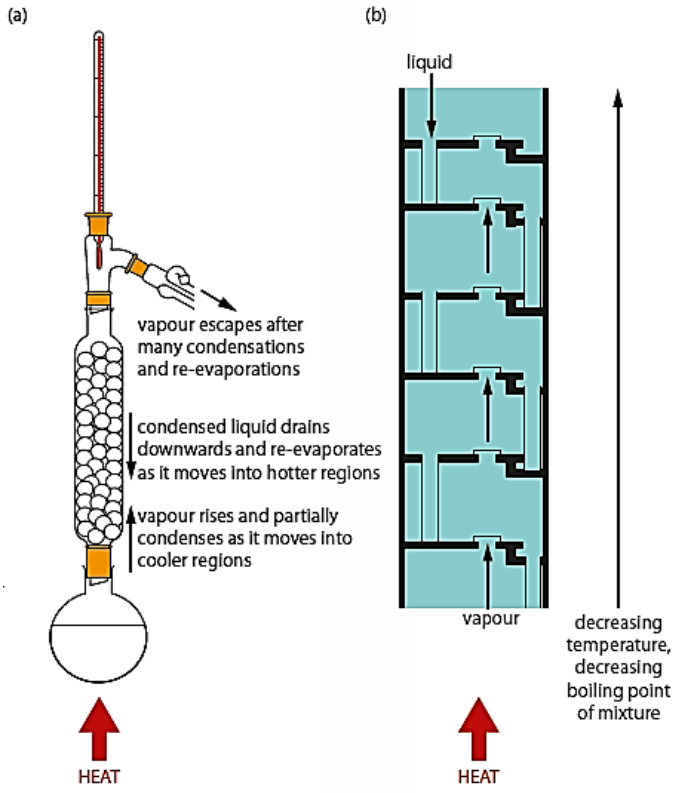


Figure 13: Columns for fractional distillation: (a) as in used in laboratories and (b) typically used in industry. Large internal surface areas maximize the area for condensation.

Calculation example:

1. A solution is prepared by mixing 0.0400 mol CH_2Cl_2 and 0.0800 mol of CH_2Br_2 at 25 °C. Assuming the solution is ideal, calculate the composition of the vapor (in terms of mole fractions) at 25 °C. At 25 °C, the vapour pressures of pure CH_2Cl_2 and pure CH_2Br_2 are 133 and 11.4 torr, respectively.

$CH_2Cl_2 \Rightarrow 0.0400\ mol / (0.0400\ mol + 0.0800\ mol) = 0.333$
$CH_2Br_2 \Rightarrow 0.0800\ mol / (0.0400\ mol + 0.0800\ mol) = 0.667$

$P_T = P°_{Cl}\ \chi_{Cl} + P°_{Br}\ \chi_{Br}$

$P_T = (133\ torr)\ (0.333) + (11.4\ torr)\ (0.667)$

$= 51.893\ torr$

Mole fraction $CH_2Cl_2 = 44.289 / 51.893 = 0.8535$
Mole fraction $CH_2Br_2 = 7.604 / 51.893 = 0.1465$