D1 - Pharmaceutical products

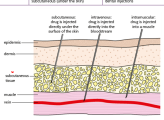
- Drug: a chemical that affects how the body works. This includes changes for the better and for the worse. The term is sometimes associated with substances which are illegal in many countries, such as cocaine, ecstasy, and heroin, but it has a broader meaning.
- Medicine: a substance that improves health. Medicines, which may be natural or synthetic, therefore contain beneficial drugs. Synthetic medicines also contain other ingredients, which are non-active but help in the presentation and administration of the drug. The beneficial effect of a medicine is known as its therapeutic effect.

The placebo effect

Problems
- Spontaneous improvement
- Fluctuation of symptoms
- Answers of politeness
- Patient misjudgement

Drug administration

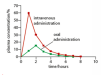
Method of administering drug	Description	Example
oral	taken by mouth	tablets, capsules, cold, liquids
inhalation	vapour breathed in; smoking	medications for respiratory conditions such as asthma; some drugs of abuse such as nicotine and cocaine
skin patches	absorbed directly from the skin into the blood	some hormone treatments, e.g. estrogen, nicotine patches
suppositories	inserted into the rectum	treatment of digestive illnesses and haemorrhoids
eye or ear drops	liquids delivered directly to the opening	treatments of infections of the eye or ear
parenteral: by injection (see figures 15.1)	intramuscular (into muscle)	many vaccines
	intravenous (into the blood, the fastest method of injection)	local anaesthetics
	subcutaneous (under the skin)	dental injections



Bioavailability of drugs: the amount that reaches the target

Not all of an administered drug reaches its target in the body. This is because the drug may be broken down in metabolic processes or may be incompletely absorbed into the blood. The fraction of an administered drug that reaches the blood supply is known as its **bioavailability**. By this definition, drugs that are administered by intravenous methods have a bioavailability of 100%, so this is used as the basis of comparison. Bioavailability is an important consideration when calculating how much of a drug to administer, known as the **dosage**.

Figure 15.2 shows a typical result of the bioavailability of a drug taken orally, compared with the same amount of the same drug taken intravenously.



First-pass effect?

20-60% of drug reaches the blood (oral administration)

Solubility - Most of blood is water → More reliability → High bioavailability

Functional groups and pH: Ought to be considered so that it is suitable for entering the blood stream/other areas of the body.

Side-effects

The overall effects of a drug in the body can be classified as follows:

physiological effects of drug in body
- therapeutic effect: the intended physiological effect
- side-effects: unintended physiological effects

Examples of side-effects:
- Drowsiness
- Nausea
- Constipation
- Damage to organs

Must be evaluated throughout drug treatment.

Thalidomide case-study:

During the early 1960s the drug thalidomide was marketed, initially in Germany, and prescribed to pregnant women in many countries to help with 'morning sickness' in their early months of pregnancy. Tragically, the drug had devastating effects on the development of the fetus, and up to 12 000 children were born with severe birth defects, most notably missing or malformed limbs, and many more did not survive infancy. By the time the deformities in the newborns were linked with the thalidomide drug, it had been widely marketed in at least 46 countries. This tragedy has led to the addition of further regulatory steps in drug licensing.

Tolerance and addiction

Tolerance: Repeated doses of a drug result in a progressively reduced response to the effects of the drug. Higher doses are needed which increases chances of toxic side-effects.

Dependence / addiction: When a patient requires a drug to feel normal. Without it they suffer from withdrawal symptoms. We can have physical and psychological dependence.

It does not need to be a prescribed medicine or illegal drug

Exercise is like an addiction. Once you're in it, you feel like your body needs it.

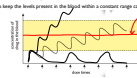
Cold turkey

Dosage

Dosage regime: The specific quantity of a drug to be taken at one time and the frequency at which this dose should be taken. Age, sex and weight are some of the factors that affect it.

Ideally the drug should be present at constant levels in the blood. This is impossible unless it is given continuously on an intravenous drip.

We must aim to keep the levels present in the blood within a constant range called therapeutic window



Via intravenous drip

The therapeutic window can be quantified as the **therapeutic index (TI)**. This is the ratio of the dose that produces toxicity to the dose that produces a clinically effective response in a population. The relevant terms in the equation are:

- The minimum effective dose, ED_{50}, is the dose that produces the therapeutic effect in 50% of the population.
- The lethal dose, LD_{50}, is the dose that is lethal to 50% of the population. This is used in animal trials.
- The toxic dose, TD_{50}, is the dose that is toxic to 50% of the population. This is used in human studies.

Units?

The therapeutic index for animals and humans is calculated using these terms to give a measure of the drugs safety. A higher value indicates a wider margin between the effective dose and the toxic one.

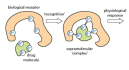
- in animals $TI = \frac{LD_{50}}{ED_{50}}$
- in humans $TI = \frac{TD_{50}}{ED_{50}}$

Higher value → High range for use of drug
Lower value → Low range for use of drug

Drug	Therapeutic effect	Therapeutic index (TI)
penicillin	antibiotic	increasing value of therapeutic index
morphine	analgesic	
cocaine	stimulant	
ethanol	depressant	
warfarin	anticoagulant in blood	

Drug action depends on interactions with receptors

The activity of a drug is determined by their ability to bind to a specific receptor in the body (usually proteins, enzymes, cell membranes or DNA). Therefore the better the fit of the drug to the receptor, the greater its activity. To bind to the receptor, a drug will usually form either ionic bonds or intermolecular forces.



The development of new synthetic drugs is a long and costly process

Why do most pharmaceutical companies focus on development of drugs for diseases such as obesity, depression and heart disease instead of rare tropical diseases?

$ $ $

Most countries have stringent controls over the development and licensing of drugs. For every new drug that reaches the market, thousands of candidate molecules fail to meet the criteria and are rejected. The average time for development of a drug from its first identification to the market is about 10–12 years.

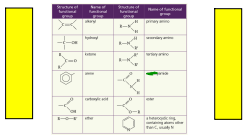
Rational drug design

Target molecule : Often a protein or enzyme found in the body that is involved with a disease.

Lead compound : A compounds that shows pharmaceutical activity with the target molecule.

Analogues : The large range of compounds that are very similar to the lead compound. Many can be tested simultaneously using combinatorial chemistry

Biological testing : Used to provide an idea of the therapeutic effect for animals.



Exercises

D2 - Aspirin and penicillin

Aspirin

Pain is detected as a sensation by the brain when nerve messages are sent from various pain receptors around the body. The receptors are stimulated by chemicals called prostaglandins. They are released by cells which have been damaged by thermal, mechanical or chemical energy. The prostaglandins can also cause dilation of blood vessels in the area and changes in body temperature (fever).

For a painkiller to work, they must block the pathway between the pain receptors and the brain.

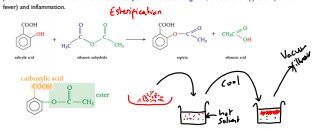
Mild analgesics such as aspirin and ibroprofen prevent stimulation of the nerve endings at the site of the pain and stop the release of prostaglandins. As these do not interfere with the functioning of the brain they are known as non-narcotics.

A strong analgesic temporarily bonds to the receptor sites in the brain, preventing the transmission of pain impulses but without depressing the central nervous system.

Development of aspirin

From the time of Hippocrates in about 400 BCE it was known that chewing willow bark could give relief to pain and fever. But it was not until the early 1800s that it was demonstrated that the active ingredient in the bark is salicin, which is converted to **salicylic acid** in the body (*salix* is the Latin name for willow). Although salicylic acid proved to be effective in treating pain, it tasted awful and caused the patient to vomit.

In 1890 the Bayer Company synthesised a more palatable derivative of salicylic acid called aspirin. It is now produced in volumes of over 100 billion tablets a year. As well as an analgesic it is also an antipyretic (reduces fever) and inflammation.

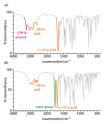


How do we synthesize it?

- Addition of conc. phosphoric acid and gentle warming.
- Isolate the aspirin product.
- Purification using recrystallisation in hot ethanol (better solvent for impurities than the aspirin).

How do we know it is aspirin?

See next page



Physiological effects of aspirin

1982 John Vane awarded Nobel Prize for discovery that analgesics block prostaglandin production in cells. It is an analgesic so also:

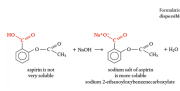
- An antipyretic (reduces fever).
- Reduces inflammation (so commonly used to treat problems with joints such as arthritis).
- One of the side-effects of aspirin is as an anticoagulant. This means it reduces the clotting ability of blood. This means it is commonly used as a prophylactic (disease prevention) by patients at risk of heart attacks and strokes. So potentially dangerous to people whose blood does not clot easily, or when blood clotting is desired (after an operation for example).

Negative side-effects:

- Irritation and ulceration of the stomach and duodenum (small intestine).
- Many people have an allergy to it.
- Has been linked to Reye's syndrome in young children (<12) - a liver and brain disorder.
- Drinking alcohol can increase the risk of these side-effects (synergistic effects).

Modification of aspirin for absorption and distribution

Formulations that contain the salt of the acid are known as soluble aspirin or dispersible aspirin.



Exercises

5 (a) Aspirin is prepared by reacting salicylic acid with excess ethanoic anhydride. In an experiment, 50.00 g of salicylic acid was converted into 55.45 g of aspirin. What was the percentage yield?
(b) How could you check the purity of your product?

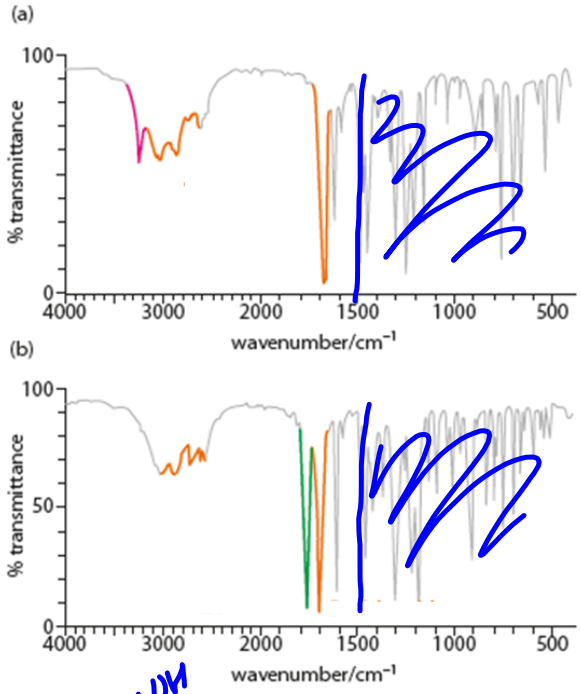
6 Describe how chemical modification of aspirin can increase its bioavailability.

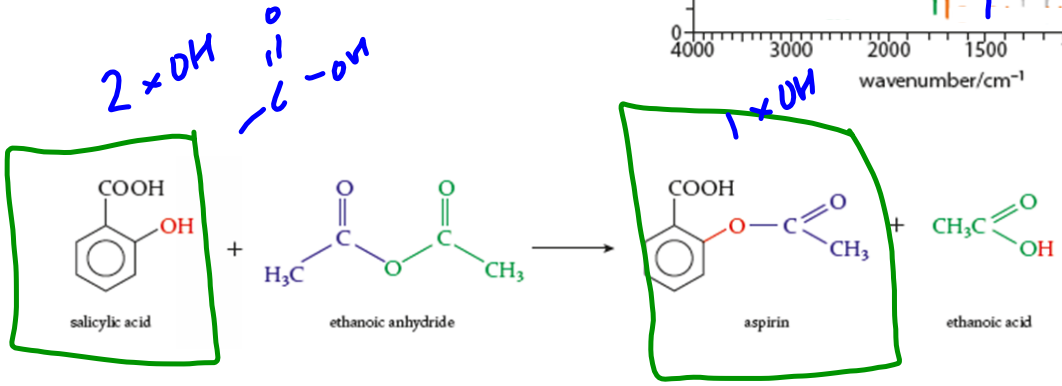
7 (a) Aspirin is described as a *mild analgesic* and as an *anticoagulant*. Explain the meaning of these two terms.
(b) Why can it be dangerous to consume alcoholic drinks when taking aspirin medication?

26. Infrared data

Characteristic ranges for infrared absorption due to stretching vibrations in organic molecules.

Bond	Organic molecules	Wavenumber (cm^{-1})	Intensity
C–I	iodoalkanes	490–620	strong
C–Br	bromoalkanes	500–600	strong
C–Cl	chloroalkanes	600–800	strong
C–F	fluoroalkanes	1000–1400	strong
C–O	alcohols, esters, ethers	1050–1410	strong
C=C	alkenes	1620–1680	medium-weak; multiple bands
C=O	aldehydes, ketones, carboxylic acids and esters	1700–1750	strong
C≡C	alkynes	2100–2260	variable
O–H	hydrogen bonding in carboxylic acids	2500–3000	strong, very broad
C–H	alkanes, alkenes, arenes	2850–3090	strong
O–H	hydrogen bonding in alcohols and phenols	3200–3600	strong, broad
N–H	primary amines	3300–3500	medium, two bands





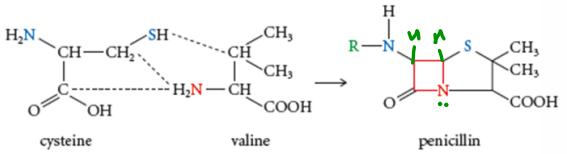
Comparisons of the spectra reveal similarities and differences between the two molecules. The major similarities in the spectra are:

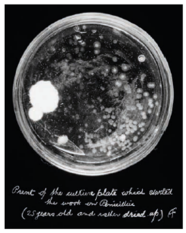
- strong peaks from 1050 to 1410 cm^{-1} due to C—O in alcohol/ester
- strong peaks from 1700 to 1750 cm^{-1} due to C=O in carboxylic acid
- both have broad peaks from 2500 to 3000 cm^{-1} due to OH in carboxylic acid
- both have peaks from 2850 to 3090 cm^{-1} due to C—H (overlapping the broad —OH peak).

Penicillin: an early antibiotic

The discovery of antibiotics

The story of penicillin

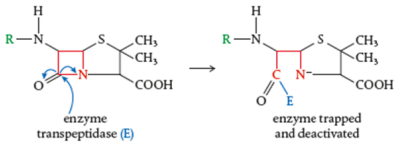




One of the key features is the amide-containing, four-membered ring (called a beta-lactam ring). The strain on the ring means that it is broken relatively easily and therefore has a high biological activity.

How does the beta-lactam ring work?:

- It breaks and binds to a bacterial enzyme, causing deactivation.
- This enzyme is responsible for cell wall formation.
- As the bacteria is unable to strengthen its cell wall, it bursts and dies.



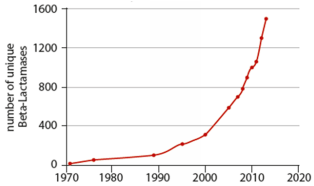
Disadvantages:

- Penicillin G (the main constituent purified from the mould) is broken down by stomach acid so had to be injected directly into the blood. We can now adapt the side chain to remove this problem.
- Many people are allergic to it.

Antibiotic resistance: bacteria fight back

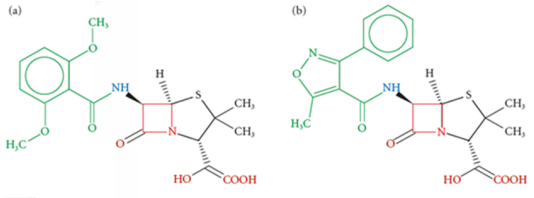
How? : Bacterial resistance to antibiotics is caused when bacteria can produce an enzyme (penicillinase or beta-lactamase that breaks the beta-lactam ring before it can deactivate the bacterial enzyme.

As antibiotic kills only the non-resistant strains, the resistant strains flourish.



How can we prevent this?

- Synthesise forms of penicillin that are able to withstand these enzymes e.g. methicillin and oxacillin. They still contain the beta-lactam ring but different side-chains.



- Control and restriction so they are not over-prescribed when other drugs can be used.
- Ensure patients take a full course of the medicine to prevent spread of the resistant strains in the community.

Exercises

8 **(a)** With reference to the structure given in section 37 of the IB data booklet, determine the molecular formula of penicillin.
(b) Mark on the molecule where the side chain can be modified and explain why this is done.
(c) Refer to the part of the molecule responsible for its antibiotic properties, and explain the basis of its mode of action.

9 Discuss three ways in which human activities have caused an increase in the resistance to penicillin in bacterial populations.

Paracetamol

Paracetamol is another commonly used analgesic . In the correct dose it is very safe but with overdoses or prolonged use it can cause:

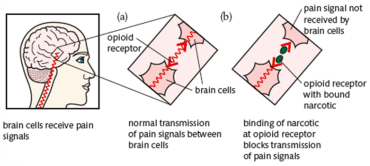
- Blood disorders
- Kidney damage
- Liver damage
- Brain damage
- Death!

D.3 Opiates

Opiates - Strong analgesics

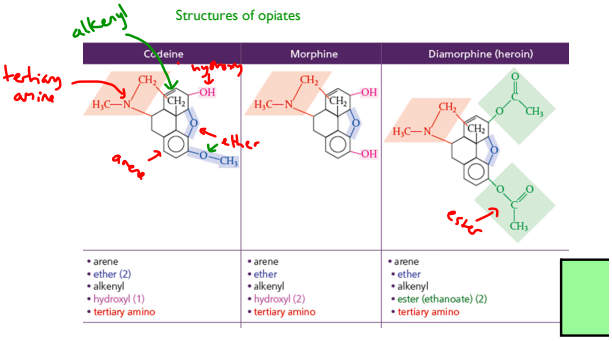
Opiates are a group of strong analgesics that work by preventing the transmission of pain impulses between opiod receptors in the brain rather than at the source.

They are natural analgesics derived from opium .



Because these analgesics act on the brain, they may cause possible changes in behaviour and mood, so they are also known as **narcotics**. Opioids are the most effective painkillers for severe pain, but due to their side-effects and potential problems with dependence, their usage must be monitored through medical supervision.

Structures of opiates



Codeine	Morphine	Diamorphine (heroin)
• arene • ether (2) • alkenyl • hydroxyl (1) • tertiary amino	• arene • ether • alkenyl • hydroxyl (2) • tertiary amino	• arene • ether • alkenyl • ester (ethanoate) (2) • tertiary amino

Heroin is classed as a semi-synthetic opiate as we must carry out 2 esterifications on the 2 OH groups of morphine to make it.

As a result of their structures and solubilities, these three drugs differ in their effectiveness as follows:

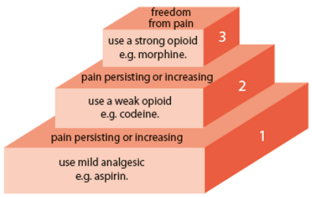
• codeine:	increasing strength as analgesics
• morphine:	increasing narcotic effects
• diamorphine:	increasing side-effects

Advantages and disadvantages of using strong analgesics

Pain management

The World Health Organization (WHO) has developed a three-step 'analgesic ladder' to be a simple guideline to encourage better global standards of pain management.

1. use mild analgesics
2. add a weak opioid such as codeine or tramadol
3. in severe intractable pain, use strong opioids such as morphine, methadone, or possibly diamorphine.



Side-effects

Strong analgesics have several other effects that can sometimes be used for therapeutic purposes, but sometimes are considered adverse side-effects. They include:

- constipation
- suppression of the cough reflex
- constriction of the pupil in the eye
- narcotic effects, which are discussed below.

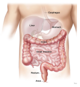
Advantages:

- Relieve acute pain
- Wide therapeutic window
- Relieve anxiety/stress
- Taken intravenously so act faster than mild analgesics

Disdvantages:

- Euphoria can induce lack of self-control
- Addication and withdrawal symptoms
- Rapidly increasing tolerance can lead to overdoses
- Kidney failure
- Transmittable diseases through needle use

D4 - pH regulation of the stomach



The gastro-intestinal tract or gut (including the stomach) has to maintain different pH environments (acidic) to control the enzyme activity.

As well as controlling enzyme activity, the low pH kills of any bacteria that enter the body via food ingestion.

Some factors such as alcohol, smoking, stress produce excess production of acidic gastric juice causing:

- Acid indigestion
- Heartburn (acid rising into the oesophagus)
- Ulceration to the gut wall

The term dyspepsia is used to refer to these kinds of pains in the upper abdomen.

Some drugs work to prevent the production of excess acid

In the 1980´s researchers discovered a bacterium, known as helicobacter, that was shown to cause stomach ulcers and had links to stomach cancer. It was found to burrow into the mucus lining of the stomach walls causing inflammation and breakdown of stomach wall tissue.

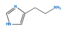
Antibiotics can now be prescribed to treat this.

The other major cause of dyspepsia is excess acid secretion. This can be treated in a number of ways:

H_2-receptor antagonists

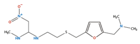
There are various mechanisms that mean acidic gastric juice is only released when required. They are stimulated by the presence of food and distension (stretching) of the stomach walls.

Of the hormones (chemical messengers) involved, histamine is of specific interest.



Histamine stimulates secretion of stomach acid by interacting with H_2 receptors, that are found in the cells that secrete HCl into the stomach. It is therefore a suitable target compound for drug interaction.

Ranitidine (Zantac) is an example of an H_2-receptor antagonist drug. It was developed from analogues of histamine using knowledge of the H_2-receptor structure, and refined from earlier drugs to increase its potency. In many countries it is now available as an over-the-counter drug, but higher dosages need prescription.



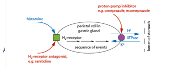
Proton pump inhibitors

In the last step of acid secretion, the parietal cells in the gastric glands pump protons (H+) across their membranes and into the lumen (open cavity) of the stomach.

To prevent charge build up, K+ ions are pumped in the opposite direction. The energy for this process is provided due to action of the enzyme called the gastric proton pump.

This enzyme is targeted by drugs such as Prilosec or Nexium deactivate this enzyme and therefore prevent acid secretion.

Summary of the action of H_2-receptor antagonists and proton pump inhibitors in reducing stomach acid secretion



Drugs to help combat excess stomach acid are known as **antacids**. They work by neutralizing the hydrochloric acid, so relieving the symptoms. Antacids are usually *weakly* basic compounds, often metal oxides, hydroxides, carbonates, or hydrogencarbonates.

- calcium hydroxide, $Ca(OH)_2$
  $Ca(OH)_2(aq) + 2HCl(aq) \rightarrow CaCl_2(aq) + 2H_2O(l)$
- magnesium hydroxide, $Mg(OH)_2$
  $Mg(OH)_2(aq) + 2HCl(aq) \rightarrow MgCl_2(aq) + 2H_2O(l)$
- aluminium hydroxide, $Al(OH)_3$
  $Al(OH)_3(aq) + 3HCl(aq) \rightarrow AlCl_3(aq) + 3H_2O(l)$

Oxides: $MgO + HCl \rightarrow MgCl_2 + H_2O$
$CaO + 2HCl \rightarrow CaCl_2 + H_2O$

- sodium hydrogencarbonate, $NaHCO_3$
  $NaHCO_3(aq) + HCl(aq) \rightarrow NaCl(aq) + H_2O(l) + CO_2(g)$
- sodium carbonate, Na_2CO_3
  $Na_2CO_3(aq) + 2HCl(aq) \rightarrow 2NaCl(aq) + H_2O(l) + CO_2(g)$

The gas released can cause bloating of the stomach and flatulence. To reduce this side-effect, antifoaming agents are often added to the formulation. Some antacids also contain alginates which float to the top of the stomach, forming a 'raft' which acts as a barrier preventing reflux into the oesophagus.

$CH_3COOH \rightleftharpoons CH_3COO^- + H^+$ $NaCH_3COO$ Na^+ CH_3COO^-

$CH_3COOH + NaOH \rightarrow NaCH_3COO + H_2O$
2 mol 1 mol 1 mol

pH and buffering

The pH of a buffer solution, that is its H^+ concentration, will depend on the interactions among its components. We will consider here an acidic buffer made of the generic weak acid HA and its salt MA.

The equilibria that exist in the buffer will be as follows.

1 weak acid: $HA(aq) \rightleftharpoons H^+(aq) + A^-(aq)$
2 salt: $MA(aq) \rightarrow M^+(aq) + A^-(aq)$

Assumptions

1 The dissociation of the weak acid is so small that it can be considered to be negligible. The equilibrium lies so far to the left that we can make the approximation:

$$[HA]_{initial} \approx [HA]_{equilibrium}$$

2 The salt is considered to be fully dissociated into its ions. The equilibrium lies so far to the right that we can make the approximation:

$$[MA]_{initial} \approx [A^-]_{equilibrium}$$

The equilibrium expression for the acid is $K_a = \frac{[H^+][A^-]}{[HA]}$

Therefore $[H^+] = K_a \frac{[HA]}{[A^-]}$

Remember that all values in this expression must be *equilibrium* concentrations.

From the approximations justified above, we know that
$[HA]_{equilibrium} \approx [HA]_{initial}$ and $[A^-]_{equilibrium} \approx [MA]_{initial}$
so we can substitute these values as follows.

$[H^+] = K_a \frac{[HA]_{initial}}{[MA]_{initial}}$, which is usually given as $[H^+] = K_a \frac{[acid]}{[salt]}$

By taking the negative logarithms of both sides of the equation, we can derive:

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

For basic buffer solutions the equivalent equations are:

$[OH^-] = K_b \frac{[base]}{[salt]}$ and $pOH = pK_b + \log_{10}\frac{[salt]}{[base]}$

A.8	$n\lambda = 2d\sin\theta$
B.7 and D.4	$pH = pK_a + \log\left(\frac{[A^-]}{[HA]}\right)$
B.7	$\log_{10}\frac{I_0}{I} = \varepsilon lc$

These are the Henderson-Hasselbalch equations. They allow us to calculate the pH or pOH of a buffer using

- the K_a or K_b values of its component acid or base and
- the ratio of initial concentrations of acid and salt used to prepare the buffer.

21. Strengths of organic acids and bases

Worked example

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

Calculate the pH of a buffer solution at 298 K, prepared by mixing 25 cm³ of 0.10 mol dm⁻³ ethanoic acid (CH_3COOH) with 25 cm³ of 0.10 cm³ sodium ethanoate ($Na^+CH_3COO^-$). K_a of $CH_3COOH = 1.8 \times 10^{-5}$ at 298 K.

Solution

pK_a of $CH_3COOH = -\log_{10}(1.8 \times 10^{-5}) = 4.74$

As there are equal volumes and concentrations of CH_3COOH and $NaCH_3COO$, then [acid] = [salt].

$pH = pK_a + \log_{10}\frac{[salt]}{[acid]} = 4.74 + \log_{10}(1) = 4.74 + 0 = 4.74$

(Note that $\log_{10}(1) = 0$)

Worked example

How would you prepare a buffer solution of pH 3.75 starting with methanoic acid (HCOOH) and NaOH?

Solution

...ic acids and bases

...tables are given in terms of pK_a where $pK_a = -\log_{10} K_a$. The dissociation constant K_a values are for aqueous at 298 K. Base strengths are given in terms of pK_b values.

Carboxylic acids

Name	Formula	pK_a
methanoic	HCOOH	3.75
ethanoic	CH_3COOH	4.76
propanoic	CH_3CH_2COOH	4.87

$pH = pK_a + \log_{10}\frac{[salt]}{[acid]}$ = 0

$HCOOH + NaOH \rightarrow NaHCOO + H_2O$
2 mol 1 mol 1 mol
Remaining 1 mol

Worked example

How much 0.10 mol dm⁻³ butanoic acid solution and solid potassium butanoate should be used to make 1.00 dm³ of pH 5.00 buffer solution? State the assumptions made in the calculation.

Solution

From the IB data booklet, butanoic acid $pK_a = 4.83$.

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

$5.00 - 4.83 = \log_{10}\frac{[butanoate\ ion]}{0.10\ mol\ dm^{-3}}$

Take anti-logs of both sides:

$10^{0.17} = \frac{[butanoate\ ion]}{0.10\ mol\ dm^{-3}} = 1.5$

[butanoate ion] = 0.15 mol dm⁻³

$pH = pK_a + \log_{10}\frac{[salt]}{[acid]}$
$0.17 = \log_{10}\frac{[salt]}{[acid]}$
$10^{0.17} = \frac{[salt]}{0.10}$
$[salt] = 0.15$ mol

Exercises

13 Suggest why the action of drugs in lowering the production of stomach acid is considered to be indirect in the case of H_2-receptor antagonists, but direct in the case of gastric proton pump inhibi...

14 Magnesium hydroxide and aluminium hydroxide can act as antacids.
(a) Write an equation for the reaction of hydrochloric acid with each of these antacids.
(b) Identify which antacid neutralizes the greater amount of acid if 0.1 mol of each antacid is used.
(c) Explain why potassium hydroxide is not used as an antacid.

15 (a) 100 cm³ of a buffer is prepared which contains 0.100 mol dm⁻³ butanoic acid and 0.200 mol dm⁻³ sodium butanoate. What is the change in pH when 2.00 cm³ of 0.100 mol dm⁻³ HCl is added to this buffer? The pK_a of butanoic acid is 4.82.
(b) How would the pH of the buffer alter if 20 cm³ of distilled water was added to the original solution?

D.5 Antiviral medications

Understandings:

- Viruses lack a cell structure and so are more difficult to target with drugs than bacteria.
- Antiviral drugs may work by altering the cells 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 preventative agents 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 IB data booklet in section 37.

Why do viruses kill?

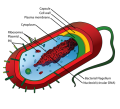
Antivirals

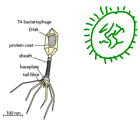
Bacteria are:

- Single-celled microorganisms.
- Have a organelles - a cell wall (made of polysaccharide molecules) and cytoplasm containing enzymes to break down food.
- Self-reproducing units.
- Able to metabolize and grow.

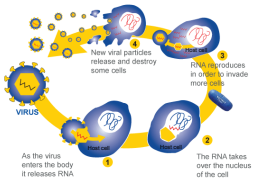
Viruses are:

- Submicroscopic
- Non-cellular particles without nucleus/cell wall/ cytoplasm etc.
- Only contain protein and nucleic acid,
- Do not feed or grow but reproduce inside the cells of living organisms (host cells).
- Have no metabolic functions.





How a Virus Works



How do antivirals work?

Body´s natural defence : Produces specific antibodies that target the virus. This provides immunity to repeated infections from the same strain of virus.

Viral infections are difficult to treat as they live within host cells and are not easily targeted. As they multiply rapidly, the chances ofmutation are high and therefore their susceptability to a drug changes quickly.

There are a number of ways that an antiviral drug works:

- Alters genetic material so that viruses cannot use it to multiply.
- Prevent viruses from multiplying by blocking enzyme activity within host cell
- Prevent viruses from entering (human) cell / bind to cellular receptors targeted by viruses.
- Prevent/hinder the release of viruses from the cell.

Antivirals can be taken as prophylactics (known as vaccines) to produce the protective antibodies for a future infection.

Ebola

Jenner and smallpox

HIV and AIDS

Aquired immune deficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV) was first diagnosed in 1981. It is transmitted through sexual or parenteral exposure to bodily fluids. Approximately 33 million people are currently HIV positive.

HIV is particularly difficult to treat as:

- It attacks CD4+T cells (white blood cells) which are the cell that usual help defend the body against viruses.
- It mutates rapidly - "more variation of HIV in a single patient than in worldwide influenze cases".
- The virus often lies dormant in host cells so no immune response is provoked.

In addition to these, the antiviral drugs used to treat HIV are relatively expensive.

There is also a range of sociocultural issues that complicates the matter:

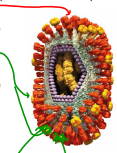
- Condom use - cost, availability, religious belief
- Cultural factors - lack of education, social stigma
- Illegal activities - drug use, prostitution
- Limited medical resources

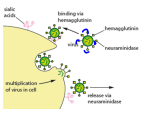
Flu viruses

Influenza, or the flu, kills aroung 500,000 people a year. Normally it´s symptoms include things like headaches and sore throats but it is particularly dangerous when contracted by people with compromised immune systems such as the elderly.

1 **Hemagglutinin (H)** is a glycoprotein that enables the viral particle to 'dock' with the host cell before it enters.

2 **Neuraminidase (N)** is an enzyme that catalyses a cleavage reaction which allows the new viral particles to escape from the host cell and spread infection. The enzyme snips off a type of sugar molecule, sialic acid, from glycoproteins on the surface of the host cell membrane.





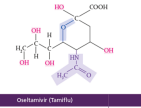
These two molecules come in a variety of subunits which control the infectivity of the virus. The naming system of viruses, such as H1N1 and H5N1, refers to the different forms of these molecules that are present.

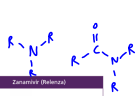
Human strain of bird flu - H7N9

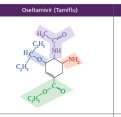
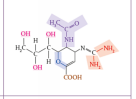
Swine flu - H1N1 and related strains

The antivirals oseltamivir (Tamiflu) and zanamivir (Relenza) both work by targeting the active site on the neuraminidase molecules.

Normally, the neuraminidase binds to the substrate sialic acid on the cell and allows viral particles to escape the host cell. These antivirals have a similar chemical structure to the sialic acid and therefore bind the active sites . Thisinhibits the normal role of the neuraminidase.





	Oseltamivir (Tamiflu)	Zanamivir (Relenza)
structure		
functional groups	alkenyl ether primary amino carboxamide / amide ester	alkenyl ether primary amino carboxamide / amide carboxylic acid hydroxyl (3)
drug action	neuraminidase inhibitor	neuraminidase inhibitor
administration	orally	inhalation
resistance to drug	some rare strains of flu virus have shown resistance	no resistance reported
counter-effects	nausea, vomiting	possible asthma

Why must these drugs be taken within 48 hours of experience the symptoms of the flu?

D.7 Taxol: a chiral auxiliary case study

Understandings:

- Taxol is a drug that is commonly used to treat several different forms of cancer.
- Taxol naturally occurs in 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:

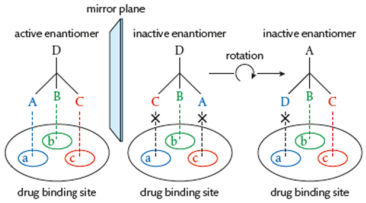
- Explanation of how Taxol (Paclitaxel) is obtained and used as a chemotherapeutic agent.
- Description of the use of chiral auxiliaries to form the desired enantiomer.
- Explanation of the use of a polarimeter to identify enantiomers.

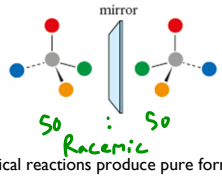
Guidance

The structure of Taxol is provided in the IB data booklet in section 37

Optical isomerism: chiral drugs exist in two forms with different activities

Optical isomers (enantiomers) usually have identical chemical properties unless they are reacting in a chiral environment (with molecules that are of only one enantiomer themselves.





Biological reactions produce pure forms of only 1 enantiomer in comparison to artificial synthesis of drugs which produce both (a racemate mixture).

The different enantiomers must be treated as different drugs as they can have very different physiological effects.

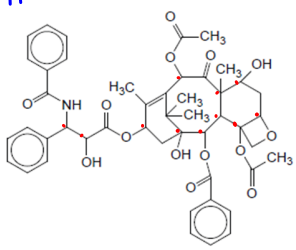
Taxol

Chemotherapy means the treatment or control of disease by chemical agents. It is generally used in the context of cancer treatment.

Taxol is a powerful anti-cancer drug from a group of compounds called taxoids . It works by preventing cell division in tumours.

It was first isolated from the bark of Pacific yew trees but there was controversy over the environmental impact of this as only 0.0004 % of the bark contains Taxol.

11 chiral centres



taxol

Nowadays, Taxol is produced as a pure enantiomer via stereospecific, or "asymmetric" synthesis.

How many chiral centres are there in this molecule?

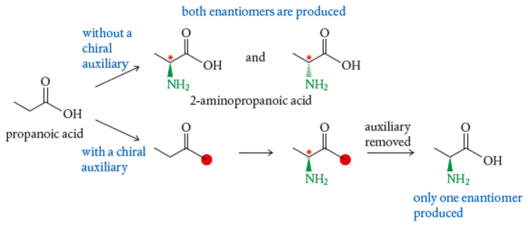
One ways of doing this is to use a chiral auxillary.

https://www.youtube.com/watch?v=PbvEd_krHI8

1. A chiral auxillary is itself an enantiomer .

2. It reacts with the reactant molecule to create the stereochemical conditions necessary to follow a certain pathway.

3. Following the reaction, the chiral auxillary is removed leaving the desired optical isomer product.



We can identifiy enantiomers using a polarimeter. By measuring the rotation of plane-polarised light, we can calculate the purity of the enantiomer.

D.8 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.
- Tracers are used in diagnostic medicine.
- Targeted alpha therapy (TAT) and boron neutron capture therapy (BNCT) are two methods which are used in cancer treatment.

Guidance

Isotopes used in nuclear medicine include Tl-99m, Ga-177, Y-90, I-131, and Rn-212.

Applications and skills:

- Discussion of common side effects from radiotherapy.
- Explanation of why technetium-99m is the most common radio isotope used in nuclear medicine based on its half-life, emission type, and chemistry.
- Explanation of why Ga-177, Y-90, and I-131 are 3 of the 10 common isotopes used for radiotherapy based on the type of radiation emitted.
- Balancing nuclear equations involving alpha and beta particles.
- Calculation of the amount of a radioisotope that has undergone decay and remaining after a certain period of time using the nuclear half-life equation.
- Explanation of TAT and how it might be used to treat diseases that have spread throughout the body.

Guidance

Common side effects discussed should include hair loss, nausea, fatigue, and sterility. Discussion should include the damage to DNA and growing or regenerating tissue.

Unstable atomic nuclei emit radiation

The stability of an atom's nucleus depends on the number and type of nuclear particles present, the so-called **nucleons**, which vary in different isotopes of the same element.

- Stable nuclei have balanced forces among the nucleons and so are not reactive.
- Unstable nuclei have unbalanced forces and an excess of internal energy, and so they spontaneously decay to form more stable nuclei, in a process known as **radioactivity**. These unstable nuclei are known as **radionuclides**.

radioactivity: unstable nucleus / radionuclide → stable nucleus + radiation: emission of particles and energy

Natural radionuclides occur in the environment in air, water, and soil. They include ^{14}C, ^{40}K, and ^{238}U. All elements with $Z > 84$ (Po onwards) and higher are naturally radioactive, which means they have no stable naturally occurring isotope.

Induced or **artificial radionuclides** are nuclei that are made to by particle-through procedures that usually involve bombardment reactions with neutrons or helium nuclei at great speed. Many radionuclides used in nuclear medicine are produced in this way.

Particle	Position	Charge	Relative mass
proton	nucleus	+	1
neutron		0	1
electron	outside nucleus	−	0.0005

When radionuclides decay into a more stable form, one of the following occurs:

The ejection of:
- A proton or a neutron (if 2 of both are released --> helium nucleus --> alpha particle)
- Energy in the form of photons known as gamma rays

The conversion of a:
- Neutron to a proton (ejecting an electron called beta particle)
- Proton to neutron (ejecting a positron)

The anti-particle of an electron

The main types of radiation are alpha, beta, and gamma

Alpha radiation

Alpha radiation is the ejection of particles from the nucleus that carry a charge of 2+ and have a mass of 4 atomic mass units. Alpha particles are equivalent to a nucleus of helium and can be denoted as ^4_2He or $^4_2\alpha$.

For example, uranium is converted into thorium by alpha decay:

$^{238}_{92}U \rightarrow {}^{4}_{2}\alpha + {}^{234}_{90}Th$

Beta radiation

When a neutron converts to a proton it releases beta radiation ($^0_{-1}\beta$ or $^0_{-1}e$). The atomic number increases by 1. The mass number remains the same, but the atomic number increases by 1.

For example, thorium is converted into protactinium by beta decay:

$^{234}_{90}Th \rightarrow {}^{0}_{-1}\beta + {}^{234}_{91}Pa$

Gamma radiation

Energy released with a wavelength in the range 0.005 to 0.1 nm is called gamma radiation. It is released due to energy changes in the nucleus so neither the mass nor atomic number are changed.

It often accompanies alpha and beta radiation.

Worked example

Write nuclear equations for the following reactions, making reference to section 5 of the IB data booklet:

(a) the alpha decay of an isotope of radon that has mass number 219

(b) the beta decay of carbon-14.

Solution

(a) Radon is Rn with $Z = 86$ so the radionuclide is $^{219}_{86}Rn$.

Alpha decay will result in a decrease in Z of 2 units and a decrease in A of 4 units. So the new element has $Z = 84$, which is polonium, Po.

$^{219}_{86}Rn \rightarrow {}^{215}_{84}Po + {}^{4}_{2}\alpha$

(b) The radionuclide carbon-14 is $^{14}_{6}C$.

Beta decay will result in an increase in Z of 1 unit and no change in A. So the new element has $Z = 7$, which is nitrogen, N.

$^{14}_{6}C \rightarrow {}^{14}_{7}N + {}^{0}_{-1}\beta$

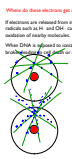
Radioactive emissions have an ionizing effect

Radioactivity is known as **ionizing radiation** because it has enough energy to interact with an atom and cause the removal of electrons, so the atom becomes ionized.

Where do these electrons get released from?

If electrons are released from inner shells in biological molecules, highly unstable radicals such as H· and OH· can be formed. This can cause rapid changes/reactions/oxidation of nearby molecules.

When DNA is exposed to ionizing radiation, the double helical structure can be broken/damaged, and base pairs or nucleotides can be lost.



Ionization density - The average energy released along a unit path length by a radioactive emission.

Gamma rays- low ionization density: produce radicals more sparsely along path

Alpha particles: high mass and charge --> high ionization density: most ionizing energy released in small region of path --> better for use a cancer treatment

Half-life of an isotope determines the rate of radioactive decay

Radioactive substances spontaneously decay at a rate that depends only on the nature of the substance. The reaction is not affected by changes in temperature, pressure, or the presence of other substances. Radioactive decay follows first-order reaction kinetics, as explained in Chapter 6.

In a first-order reaction for a reactant N, the rate expression is:

$rate = k[N]$

Half-life, $t_{\frac{1}{2}}$ - time taken for the [reactant] to reach half its original value

C.3 and D.8	$t_{\frac{1}{2}} = \frac{\ln 2}{\lambda}$

The data booklet contains the following formula containing lambda --> the decay constant (rate constant)

Figure 15.30 Radioactive decay of Tc-99m, showing its half-life of 6 hours

Worked example

An isotope of radium, ^{226}Ra, has a half-life of 1620 years. Calculate the rate constant for the decay of radium-226.

Solution

Substitute the given value for $t_{\frac{1}{2}}$ into the equation $k = 0.693/t_{\frac{1}{2}}$

$k = \frac{0.693}{1620 \text{ years}} = 4.28 \times 10^{-4} \text{ year}^{-1}$

Note that the units of the rate constant of a first-order reaction are time^{-1}, and the units of time in this solution must be consistent with those for the half-life.

If we consider the graph of technetium-99m (see Figure 15.30), from the fact that $t_{\frac{1}{2}} = 6$ hours, we can deduce that

- after one half-life, 6 hours, 50 % of the original sample remains
- after two half-lives, 12 hours, 25 % of the original sample remains
- after three half-lives, 18 hours, 12.5 % of the original sample remains, etc.

It follows that if a known set of 6 hours are allowed to pass, the amount remaining will be 0.5 of the original amount. This means that

$\frac{N_t}{N_0} = (0.5)^n$ where:

$\frac{N_t}{N_0}$ = proportion of isotope remaining

n = number of half lives = $\frac{t}{t_{\frac{1}{2}}}$

N_0 : initial amount of radioisotope

We can use this equation to calculate the amount of isotope decayed and remaining at any interval of time, from knowledge of either the half-life or the decay constant.

D.8	$M(t) = N_0\left(\frac{1}{2}\right)^{\frac{t}{t_{\frac{1}{2}}}}$

Worked example

What amount of ^{99}Tc will be left when 5.65 mol of this isotope is allowed to decay for 15.0 min? The half-life of ^{99}Tc is 25.0 min.

Solution

number of half-lives = $\frac{15.0 \text{ min}}{25.0 \text{ min}} = 0.6$

$\frac{N_t}{N_0} = (0.5)^{0.6}$

proportion remaining = $(0.5)^{0.6} = 0.6597$

∴ amount remaining = 5.65 mol × 0.6597 = 2.41 mol

As a quick check, it is obvious that the time interval is less than a half-life, so it makes sense that the amount remaining is more than half the original amount.

Nuclear radiation in medical treatment

'Nuclear medicine' refers to the use of radiation in healthcare practice, which is now a major part of medical care in two main areas:

- in the diagnosis of disease, by helping to provide detailed information about an individual's internal organs – the techniques used are known as **nuclear imaging**
- in the treatment of disease, particularly cancer, through the destruction of targeted cells – this is known as **radiotherapy**.

Diagnostic techniques:

1. Make a tracer. Attach a radionuclide to a biological active molecule (radiopharmaceutical) that targets a certain part of the body.

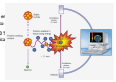
E.g. Iodine taken up by thyroid gland. Glucose taken up by brain.

2. Taken orally or by injection.

3. Gamma radiation can be detected by a gamma camera as it passes through body.

Requirements:
- The gamma radiation must be e
- The $t_{\frac{1}{2}}$ must be long enough to

Technetium-99 is used in about 80 % half-life, low radiation dose, chemica



Positron emission tomography (PET)

A three-dimensional diagnostic technique

1. Tracer - usually fluorine-18 bonded to a glucose molecule.
2. The fluorine radionuclide releases a positron.
3. Positron immediately hits an electron and this releases gamma radiation.
4. Gamma radiation detected by gamma camera.

Cancer cells have a different uptake of glucose to normal cells.

Magnetic resonance imaging (MRI)

Uses ^1H NMR spectroscopy:

1. Single proton in H nucleus can "flip" to higher spin state by exposure to radio waves.
2. As body is 70 % water, this allows detail imaging of parts of the body.
3. As radiowaves have a large wavelength (low frequency) they are not considered ionising radiation and do not harm living cells.

Why do we not call it something to do with NMR?

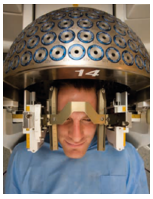
Radionuclide therapy

Cancer is one of the largest causes of death globally. It is caused when cells lose the ability to control growth and division --> causing tumours . The ionising effect of radiotherapy mostly affects the DNA responsible for this process so is used alongside chemotherapy and surgery to treat tumours.

To treat tumours, we must target the cancerous cells and minimise damage to normal cells:

An ideal radionuclide are strong beta-emitters (to damage cancerous cells) that also emit enough gamma radiation (so that they can be traced with imaging)

Most common --> Lutetium-177 and yttrium-90



1 External radiotherapy or teletherapy

External source of radiation is targeted at specific sites of cancer. E.g.

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

2 Internal radionuclide therapy

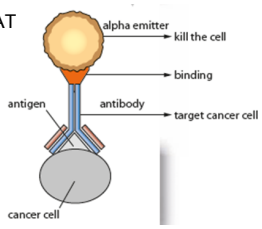
A radioactive material is taken in the body in solid form or as aliqud:

- A wire, seed or tube implanted near tumour site.
- Oral/parenteral administration - e.g. iodine-131 for thyroid cancer

Current development of radoinuclide therapy - targeted alpha therapy :

- Used to treat dispersed cancers (metastasis) e.g pancreatic, ovarian, melanoma
- TAT uses alpha-emitters that specifically target canercous cells
- Radionuclide attached to antibody that fits antigen of cell

TAT



Alpha particles - high ionizing density yet radiation range is short so minimal damage to other cells.

Pb-212 is currently being researched for this purpose.

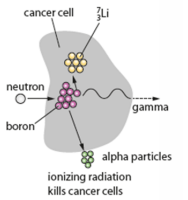
Boron Neutron Capture Therapy

BNCT

A currently developing use of radionuclide therapy:

- Non-radioactive boron-10 administered - collects in brain tumour cells
- Neutrons fired at boron
- Unstable boron nucleus undergoes alpha decay (and release of gamma radiation)
- Alpha particles destroy cancerous cells

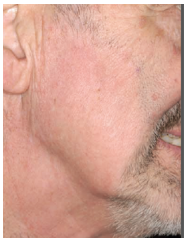
$$^{10}_{5}\text{B} + {}^{1}_{0}\text{n} \rightarrow {}^{11}_{5}\text{B} \rightarrow {}^{4}_{2}\alpha + {}^{7}_{3}\text{Li}$$



Side-effects of radiotherapy

As with all forms of medical treatment, individuals vary greatly in their responses to radiotherapy, but some of the most common side-effects are:

- fatigue – rest and regular hydration are important during treatment
- nausea – more common when the treatment is in the area of the digestive system
- hair-loss – this occurs within the treatment area and is usually temporary
- sterility – more likely if treatment is close to ovaries or testes
- skin reaction – skin may become red, sore, or itchy in local area of irradiation.



Atomic number 39

Exercises

22 **(a)** Formulate the nuclear equation for the decay of ^{90}Y, which is a beta emitter.
(b) The ^{90}Y isotope has a half-life of 64 hours. Calculate how much of a 65.0 g sample would remain after 4 days.

23 ^{228}Ac is radioactive. After one day it is found that 0.33 mg of a 5.0 mg sample remains. What is its half-life?

24 **(a)** Outline the characteristics of Tc-99m that make it so suitable for use in diagnostic procedures.
(b) State the characteristics of Lu-177 and Y-90 that make them useful in radiotherapy.

25 **(a)** Describe what is meant by targeted alpha therapy.
(b) Explain two characteristics of alpha particles that enable them to be particularly effective in cancer treatments.

22 (a)

$^{90}_{39}Y \rightarrow {}^{90}_{40}Zr + {}^{0}_{-1}\beta$

(b)

24 (a) Half-life is 6 hours – long enough for diagnosis but decays quickly. Radiatic gamma rays used for detection and lc energy electrons which minimize radia

(b) Strong beta emitters that also emit gamma radiation to enable imaging.

D.9 Drug detection and analysis

Understandings:

- Organic structures can be analysed and identified through the use of infrared spectroscopy, mass spectrometry 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 breathalyser.

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 fractional distillation and purification of an organic product. Consider the use of fractional distillation, Raoult's law, the properties on which mixtures 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 breathalyser.

Guidance

- *Students should be able to identify common organic functional groups in a given compound by recognition of common stable structures and from IR (section 26 of the data booklet) 1H NMR (section 27 of the data booklet), and mass spectral fragments (section 28 of the data booklet) data.*
- *A common retinal structure is provided in the data booklet (section 30).*

Drug isolation and purification

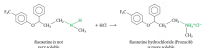
Purification of a product from the mixture of compounds produced in a chemical reaction is based around 2 major properties:

- differences in solubilities in different solvents
- differences in volatility.

LIKE DISSOLVES LIKE

Compounds with long carbon chains and aromatic rings are more soluble in non-polar solvents.
High numbers of functional groups such as OH, COOH and NH_2 are more soluble in polar solvents like water.

A conversion of a compound to an ionic salt increases solubility in water:



fluoxetine is not very soluble

fluoxetine hydrochloride (Prozac®) is more soluble

Decaf coffee

Extraction : isolation of a compound using solubility differences.

When a solute is exposed to 2 solvents, it will dissolve unequally in them depending on its solubility in both. This process of partition allows us to use solvent extraction.

- A product mixture is an aqueous solution that contains the required product X. It is known that X has a higher solubility in hexane than in water.
- The aqueous mixture is added to a **separating funnel** and a volume of hexane is added. The funnel is shaken vigorously and then placed in a stand to allow the contents to settle. Hexane is less dense than water and so forms the upper layer.
- Product X has dissolved more in the hexane than the water. The lower aqueous layer can be drained away, leaving the hexane layer containing X in solution.
- X can then be recovered by evaporation of the hexane.

Solvent extraction is used in the preparation of pencillin. The drug is extracted from aqueous solution using trichloromethane as the solvent.

Organic structure and volatility

- Molecular size: volatility lowers with increasing molecular size due to increases in the London (dispersion) forces.
- Polarity: more polar functional groups cause lower volatility due to their ability to form hydrogen bonds or dipole–dipole interactions. The influence of functional groups on lowering volatility is in the order:

amide > carboxyl > hydroxyl > ketone > aldehyde > amino > ester > ether

Fractional distillation exploits differences in volatility.

The underlying law that explains the use of fractional distillation is Raoult's Law .

Using *P* for vapour pressure:

$$P_{total} = P_A + P_B$$

The vapour pressures of each component, P_A and P_B, are calculated by **Raoult's law**. This states that the vapour pressure of a volatile substance in a solution is equal to the vapour pressure of the pure substance multiplied by its mole fraction in the solution.

Using P^* to represent the vapour pressure of a pure substance:

$$P_A = P^*_A \times \chi_A \text{ and } P_B = P^*_B \times \chi_B$$

$$P_{total} = P_A + P_B = P^*_A \times \chi_A + P^*_B \times \chi_B$$

This is only true for ideal solutions in which the 2 liquids are fully miscible

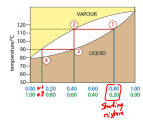
Total pressure = Partial pressure A + Partial pressure B

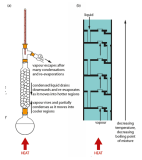
$\chi_A = \frac{\text{moles of A}}{\text{Total moles}}$

Raoult's Law can be summarised in the following graph:

- x represents the solutions when it contains equal amounts of each component A and B – the mole fraction of each is 0.5.
- y represents the total vapour pressure of that equimolar mixture. This shows that B makes a larger contribution to the total vapour pressure than A, as the vapour must contain a higher proportion of molecules of B.

Fractional distillation is an application of Raoult's law. When a solution boils, it produces a vapour which is enriched in its more volatile component. When that vapour is collected, it condenses to form a solution which is also enriched in the more volatile component. By repeating the cycle of boiling and condensation, more and more separation of the components can be achieved.





Crude oil

Drug detection

http://www.bbc.com/sport/athletics/35298526

Steroid detection

Steroids are lipids with a structure consisting of four fused rings, known as a steroidal backbone. An example of a steroid is cholesterol, which has the following structure:

Steroids are found in some hormones and promote tissue, specifically in muscles –> increasing strength and endurance.

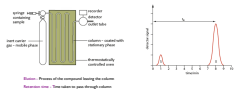
Harmful physiological effects:

- Toxic to liver
- Associated with cancer and heart problems
- Disturb hormone balance in the body
- Fertility problems.

The most common method used for detection of steroids in blood and urine samples is known as gas chromatography–mass spectrometry, GC-MS. This uses the two techniques of chromatography and mass spectrometry combined in sequence:

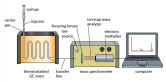
- gas chromatography separates the chemical mixtures into pure chemicals
- mass spectroscopy identifies and quantifies the components.

- stationary phase – a microscopic layer of a non-volatile liquid, usually a polymer, which is coated on the walls of an inert solid support
- mobile phase – an inert carrier gas, such as helium.



Elution – Process of the compound leaving the column.
Retention time – Time taken to pass through column.

Mass spectrometry : **Can be used directly after elution to identify compounds.**



Detecting ethanol

Alcohol is a depressant meaning it decreases the activity of the CNS causing short-term changes and long-term dependency.

As a person 's judgement is impaired after drinking alcohol, legal limits are set for ethanol concentration (Blood Alcohol Concentration - 80 mg per 100 mL) in the blood in activity such as driving. There are several ways methods for measuring these levels via the breath , blood and urine .

- Breathalysers

Ethanol is a volatile compound and so establishes equilibrium in the lungs between the solution in the blood and gas, which is released in exhaled breath.

$$C_2H_5OH_{(aq)} \rightleftharpoons C_2H_5OH_{(g)}$$

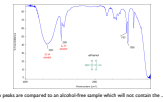
in blood — in exhaled breath

The equilibrium constant K_c for this reaction has a fixed value at a particular temperature so measurement of ethanol in the breath can be used to assess the blood alcohol concentration. Instruments that measure ethanol concentration in a sample of breath and convert it into blood alcohol concentration are known as **breathalysers**.

The extent of the colour change in this reaction can be measured using a photocell .

After an initial breathalyser test, the test must be confirmed by the use of an intoximeter . One type of intoximeter uses an infrared spectrophotometer that produces a spectrum depending on the types of bonds present in a sample.

IR energy causes vibrations in bonds depending on the mass of the atoms and height/strength of the bonds.



The absorption peaks are compared to an alcohol-free sample which will not contain the C–H peak.

The second type of intoximeter (or alcosensor) contains a fuel cell to measure the ethanol concentration. It consists of 2 platinum electrodes and a porous acid electrolyte between them. Exhaled air moves through the electrolyte and is oxidised at the anode:

$$C_2H_5OH_{(g)} + H_2O_{(l)} \rightarrow CH_3COOH_{(l)} + 4H^+_{(aq)} + 4e^-$$

Protons and electrons released from this reaction pass to the cathode where they reduce oxygen to water.

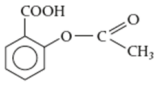
$$O_{2(g)} + 4H^+_{(aq)} + 4e^- \rightarrow 2H_2O_{(l)}$$

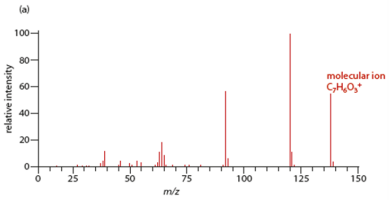
The overall reaction is the oxidation of ethanol to ethanoic acid and water.

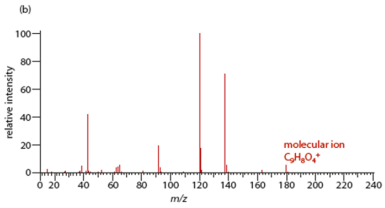
$$C_2H_5OH_{(g)} + O_{2(g)} \rightarrow CH_3COOH_{(l)} + H_2O_{(l)}$$

Organic structure analysis and identification

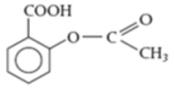
Mass spectrometry

Salicylic acid $C_7H_6O_3$	Aspirin $C_9H_8O_4$
	
molecular ion $C_7H_6O_3^+$ $m/z = 138$	molecular ion $C_9H_8O_4^+$ $m/z = 180$





^{1}H NMR spectroscopy - How many peaks would be expected and with what splitting?



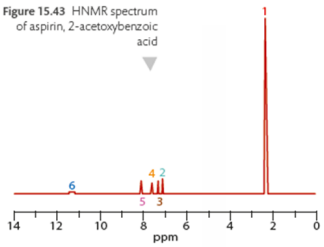
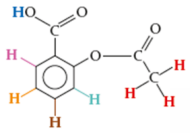
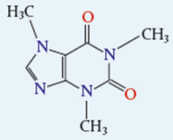


Figure 15.43 HNMR spectrum of aspirin, 2-acetoxybenzoic acid

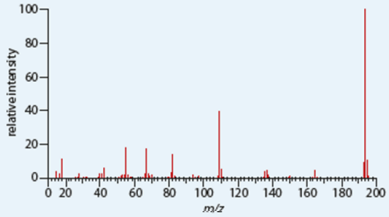


Peak	Chemical shift / ppm	Type of proton	Splitting pattern
1	2.3	3 equivalent protons on the $-CH_3$ group in the ester group	singlet
2	range 7–8	4 protons attached within the aromatic ring, each in slightly different chemical environments	doublet
3			triplet
4			triplet
5			doublet
6	11	–OH of carboxylic acid; but the peak is so broad that it is almost not visible	singlet

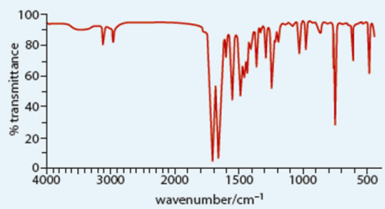
29 Caffeine has the following structure:



(a) In the mass spectrum given in Figure 15.46, what peak supplies the strongest evidence for the presence of caffeine?



(b) Identify two characteristic absorptions in the infrared spectrum (Figure 15.47) that are consistent with the structure of caffeine.



(c) How many peaks would you expect in the ^{1}H NMR spectrum of caffeine? What would be their relative areas and splitting patterns?

(d) Name three functional groups present in caffeine.

D.6 Environmental impact of some medications

Understandings:

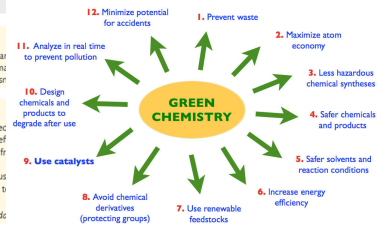
- High-level waste (HLW) is waste that gives off la
- Low-level waste (LLW) is waste that gives off sma
- Antibiotic resistance occurs when microorganisr

Applications and skills:

- Description of the environmental impact of mec
- Discussion of environmental issues related to lef
- Explanation of the dangers of antibiotic waste, fr the development of antibiotic resistance.
- Discussion of the basics of Green Chemistry (sus
- Explanation of how Green Chemistry was used t

Guidance

The structure of oseltamivir is provided in the IB da



Anastas and Warner (1998)

Solvent waste: the major emission of the drug industry

Solvent use is therefore a serious concern in the pharmaceutical industry. The suitability of solvents can be assessed by three factors:

1. toxicity to workers – whether the solvent is carcinogenic (cancer causing) or associated with other health issues
2. safety of the process – whether the solvent is highly flammable, explosive, or can cause toxic by-products
3. harm to the environment – whether the solvent will contaminate soil and ground water, cause ozone depletion, or contribute to greenhouse gas formation when released or burned.

On the basis of these criteria, examples of some common solvents can be classified as preferred or undesirable as shown below.

Preferred solvents	**Undesirable solvents**
water, H_2O	dichloromethane, CH_2Cl_2
ethanol, C_2H_5OH	methanal, HCHO
2-propanol, $CH_3CH(OH)CH_3$	tetrachloromethane, CCl_4
propanone, CH_3COCH_3	diethyl ether, $C_2H_5OC_2H_5$
ethyl ethanoate, $CH_3COOC_2H_5$	benzene, C_6H_6

Nuclear waste: an increasing problem in the drug industry

High-level waste - Large amounts of ionizing radiation for a long time: Radioisotopes used in medical procedures.

Storage- 5/10 years in cooling ponds and then to dry storage in heavily shielded structures underground.

Low-level waste - Small amounts of ionizing radiation for a short time: clothing, protective shoe covers, paper towels etc.

Storage- Sealed in containers and placed in landfill once decayed.

Antibiotic waste: are we killing the cures?

Superbugs - antibiotic resistant bacteria that carry several resistant genes. E.g. MRSA

Overuse of antibiotics and the millions of tonnes of antibiotic compounds have been released into the biosphere, increasing exposure of them to bacteria.

Non-human uses include:

- therapeutic use in aquaculture and household pets
- growth promotion and prophylactic use in animal livestock
- pest control in agriculture
- sanitizers in toiletries and household cleaning products
- sterilization and culture selection in research and industry.

Solutions :

- Strict control measure for use of antibiotics
- Suitable destruction before disposal

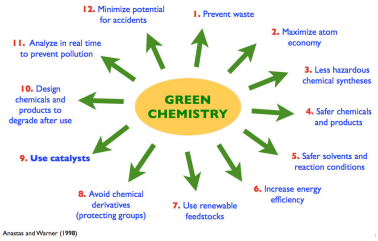
Obtaining the Tamiflu precursor: a Green Chemistry case study

The key precursor for the synthesis of Tamiflu is **shikimic acid**, or its salt shikimate, with the following structure:

Mostly harvested from the star anisefound in SW China and Vietnam BUT lengthy extraction process with low yield.

Green chemistry approach:

- Production of shikimate from fermentation reactions of geneticall engineered bacteria.
- Harvesting from a range of pine needles that are more abundant that the star anise
- Extraction from suspension cultures of the Indian sweetgum tree.



Anastas and Warner (1998)

- The production of the drug Viagra by Pfizer uses a modified reaction route that produces just a quarter of the waste of the original process. It reduces the amount of solvent and avoids the use of toxic and hazardous reagents.
- The synthesis of the anti-inflammatory drug ibuprofen has been altered from a six-step to a three-step reaction route. This has increased the atom economy of the process from 40% to 77% and reduced the energy demand.
- Synthesis of the analgesic drug Lyrica was modified to use a natural reagent of an enzyme with water as a solvent to reduce the use of non-renewable organic materials. This has eliminated the emissions of more than 3 million tonnes of CO_2 compared with the original process.