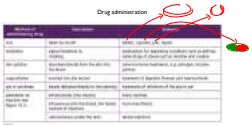
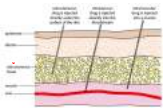
D1 - Pharmaceutical products

The placebo effect

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

Drug administration





Bioavailability of drugs: the amount that reaches the target

First-pass effect?

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

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

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

Side-effects

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

Must be evaluated throughout drug treatment.

Thalidomide case-study

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

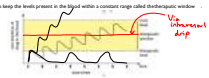
Cold turkey

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 thetherapeutic window



Via intravenous drip

Units?

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

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

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 cure tropical diseases?

$ $ $

More countries have stringent controls over the development and licensing of drugs. for every one 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

Therapeutic index for animals = $\frac{LD_{50}}{ED_{50}}$

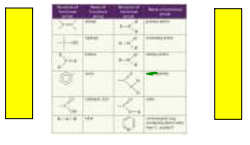
"Double-blind test"

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.



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.

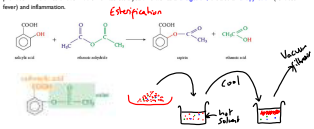
Mild analgesics such as aspirin and ibroprofen prevent stimulation of the nerve endings at the site of the pain and stop the release of prostaglandins. As these do not interfere with the functioning of the brain they are known as non-narcotics.

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.

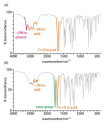


How do we synthesize it?

- 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).

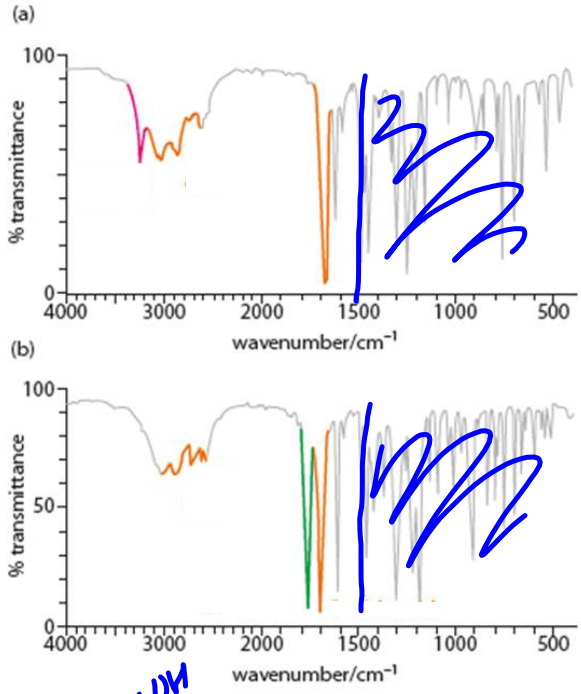
Modification of aspirin for absorption and distribution

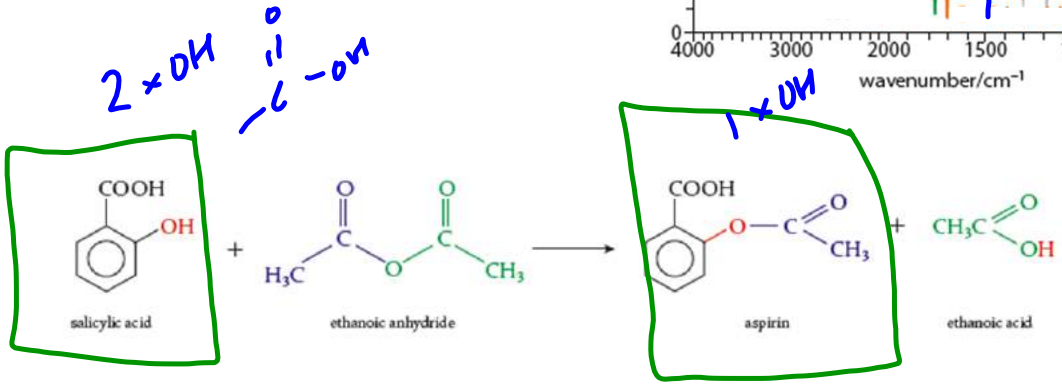
Exercises

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





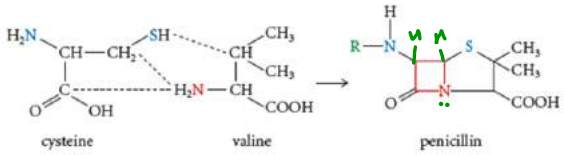
Comparisons of the spectra reveal similarities and differences between the two molecules. The major similarities in the spectra are:

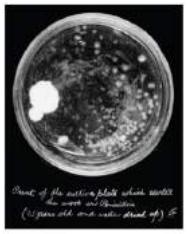
- strong peaks from 1050 to 1410 cm^{-1} due to C—O in alcohol/ester
- strong peaks from 1700 to 1750 cm^{-1} due to C=O in carboxylic acid
- both have broad peaks from 2500 to 3000 cm^{-1} due to OH in carboxylic acid
- both have peaks from 2850 to 3090 cm^{-1} due to C—H (overlapping the broad —OH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

Penicillin: an early antibiotic

The discovery of antibiotics

The story of penicillin

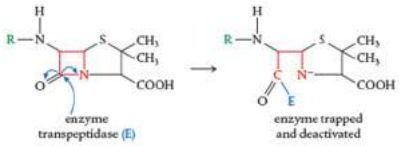




One of the key features is the amide-containing, four-membered ring (called a beta-lactam ring). The strain on the ring means that it is broken relatively easily and therefore has a high biological activity.

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.



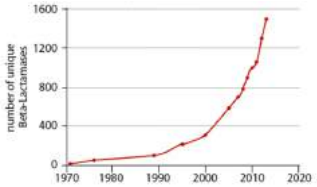
Disadvantages:

- 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

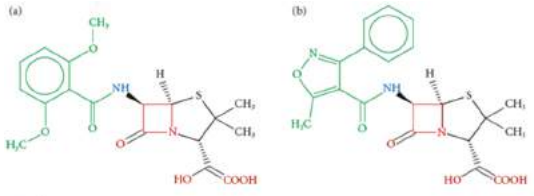
How? : Bacterial resistance to antibiotics is caused when bacteria can produce an enzyme (penicillinase or beta-lactamase that breaks the beta-lactam ring before it can deactivate the bacterial enzyme.

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:

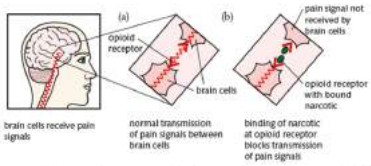
- Blood disorders
- Kidney damage
- Liver damage
- Brain damage
- Death!

D.3 Opiates

Opiates - Strong analgesics

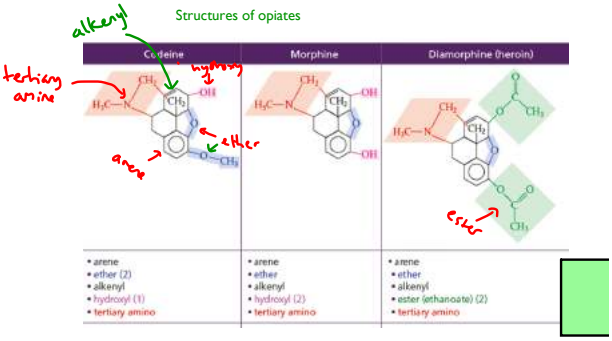
Opiates are a group of strong analgesics that work by preventing the transmission of pain impulses between opiod receptors in the brain rather than at the source.

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



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.

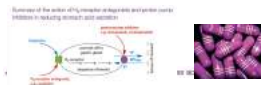
Ranitidine (Zantac) is an example of an H_2-receptor antagonist drug. It was developed from analogues of histamine using knowledge of the H_2 receptor structure, and refined from earlier drugs to increase its potency. In many countries it is now available as an over-the-counter drug, but higher dosages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

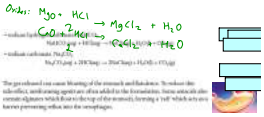
To prevent charge build up, K^+ ions are pumped in the opposite direction. The energy for this process is provided due to action of the enzyme called the gastric proton pump.

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



Drugs to help combat excess stomach acid are known as antacids. They work by neutralising the hydrochloric acid, so relieving the symptoms. Antacids are usually made from a compound(s), often metal oxides, hydroxides, carbonates, or hydrogencarbonates.

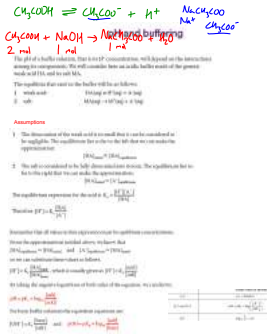
- calcium hydroxide, $Ca(OH)_2$: $Ca(OH)_2(aq) + 2HCl(aq) \rightarrow CaCl_2(aq) + 2H_2O(l)$
- magnesium hydroxide, $Mg(OH)_2$: $Mg(OH)_2(aq) + 2HCl(aq) \rightarrow MgCl_2(aq) + 2H_2O(l)$
- aluminium hydroxide, $Al(OH)_3$: $Al(OH)_3(aq) + 3HCl(aq) \rightarrow AlCl_3(aq) + 3H_2O(l)$



Overall: $MgO + 2HCl \rightarrow MgCl_2 + H_2O$

$CaO + 2HCl \rightarrow CaCl_2 + H_2O$

The gas released can cause 'bloating' of the stomach and flatulence. To reduce this side-effect, anti-foaming agents are often added to the formulations. 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.



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

$CH_3COOH + NaOH \rightarrow NaCH_3COO + H_2O$

2 mol $\quad$ 1 mol $\quad$ 1 mol

Acetate buffers

Assumptions

1 The dissociation of the weak acid is so small that it can be considered to be negligible. The equilibrium for acids to the left that we can make the approximation that $[HA]_{equil} = [HA]_{solution}$

2 The salt is considered to be fully dissociated in solution. The equilibrium for it to the right that we can make the approximation that $[A^-]_{equil} = [A^-]_{solution}$

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 equation must be equilibrium concentrations.

From the approximations detailed above, we know that $[HA]_{equilibrium} = [HA]_{acid}$ and $[A^-]_{equilibrium} = [HA]_{salt}$ so we can substitute these values as follows:

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

By taking the negative logarithms of both sides of the equation, we a acidity:

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

For basic buffers solutions the equivalent equations are:

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

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

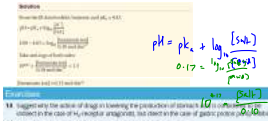
- K_a or K_b values of its component acid or base and
- the ratio of initial concentrations of acid and salt used to prepare the buffer.

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

$HCOOH + NaOH \rightarrow NaHCOO + H_2O$

2 mol $\quad$ 1 mol $\quad$ 1 mol

Remaining 1 mol



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

$0.17 = \log_{10} \frac{[salt]}{[acid]}$

D.5 Antiviral medications

Understandings:

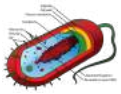
Applications and skills:

Why do viruses kill?

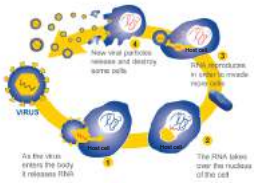
Antivirals

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.

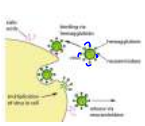
There is also a range of sociocultural issues that complicates the matter:
- Condom use - cost, availability, religious belief
- Cultural factors - lack of education, social stigma
- Illegal activities - drug use, prostitution
- Limited medical resources

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 **Haemagglutinin** (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.

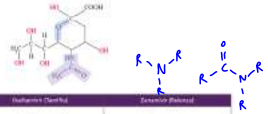


There two molecules come in a variety of subunits which control the infectivity of the virus. The naming system of viruses, such as H1N1 and H5N1, refers to the different forms of these molecules that are present.

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, carboxylate / amide	alkenyl, ether, primary amino, carboxylate, carboxylic acid (without H), guanidine / amide
drug action	neuraminidase inhibitor	neuraminidase inhibitor
administration	orally	inhalation
resistance to drug	some new strains of flu virus have shown resistance	no resistance reported
side-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:

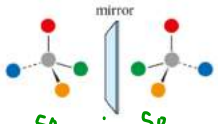
- Explanation of how Taxol (Paclitaxel) is obtained and used as a chemotherapeutic agent.
- Description of the use of chiral auxiliaries to form the desired enantiomer.
- Explanation of the use of a polarimeter to identify enantiomers.

Guidance

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

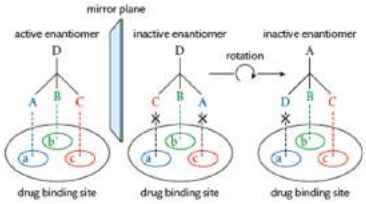
Optical isomerism: chiral drugs exist in two forms with different activities

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.



So : So

Racemic



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.

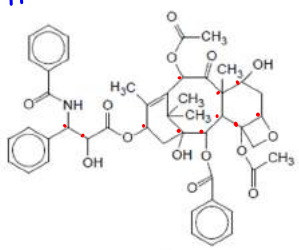
Taxol

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?

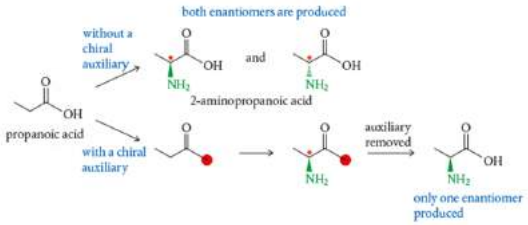
One ways of doing this is to use a chiral auxillary.

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

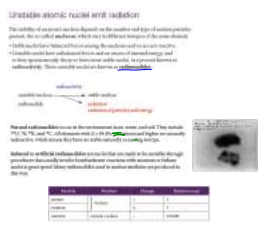
1. A chiral auxillary is itself an enantiomer .

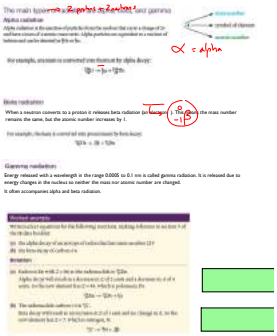
2. It reacts with the reactant molecule to create the stereochemical conditions necessary to follow a certain pathway.

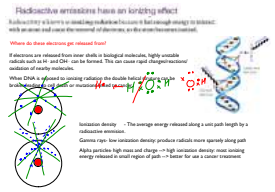
3. Following the reaction, the chiral auxillary is removed leaving the desired optical isomer product.

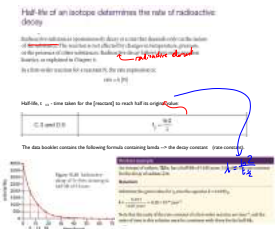


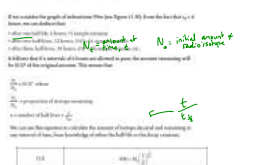
We can identifiy enantiomers using a polarimeter. By measuring the rotation of plane-polarised light, we can calculate the purity of the enantiomer.

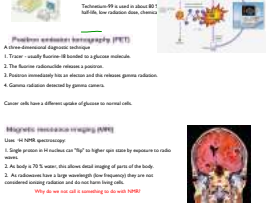












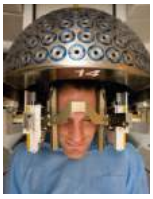
Radionuclide therapy

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.

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

2 Internal radionuclide therapy

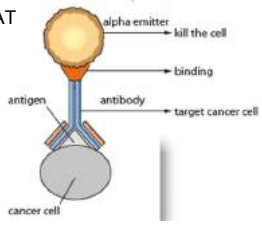
A radioactive material is taken in the body in solid form or as aliqud:

- 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.

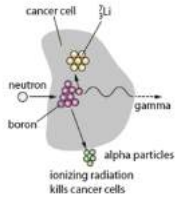
Boron Neutron Capture Therapy

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

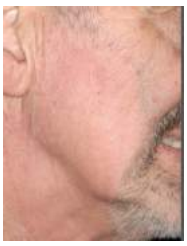
$$^{10}_{5}B + ^{1}_{0}n \rightarrow ^{11}_{5}B \rightarrow ^{4}_{2}\alpha + ^{7}_{3}Li$$



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 lo energy electrons which minimize radia

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

min

D.9 Drug detection and analysis

Understandings:

Applications and skills:

Drug isolation and purification

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

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:

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.

Organic structures and volatility

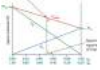
Fractional distillation : exploits differences in volatility.

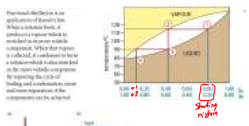
The underlying law that explains the use of fractional distillation is Raoult's Law .

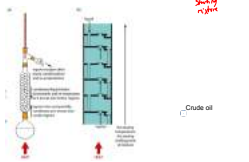
This is only true for ideal solutions : in which the 2 liquids are fully miscible

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:







Crude oil

Drug detection

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

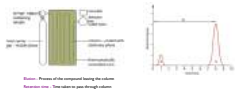
Blood detection:

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

Harmful physiological effects:

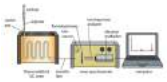
- Toxic to liver
- Associated with cancer and heart problems
- Disturb hormone balance in the body
- Fertility problems.

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



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

Mass spectrometry : Can be used direct 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.

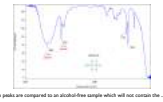
As a person 's judgement is impaired after drinking alcohol, legal limits are set for ethanol concentration (Blood Alcohol Concentration - 80 mg per 100 mL) in the blood in activity such as driving. There are several ways methods for measuring these levels via the breath , blood and urine .

- Breathalysers

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 length/strength of the bonds.

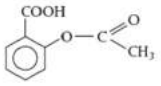


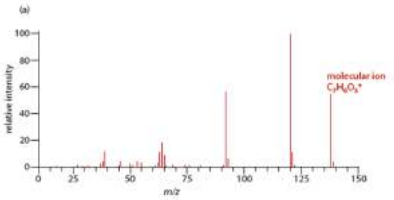
The absorption peaks are compared to an alcohol-free sample which will not contain the C−H peak.

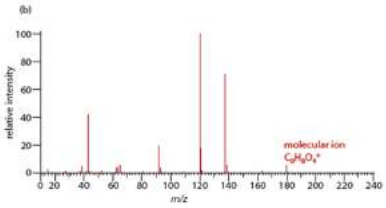
The second type of intoximeter (or alcosensor) contains a fuel cell to measure the ethanol concentration. It consists of 2 platinum electrodes and a porous acid electrolyte between them. Exhaled air moves through the electrolyte and is oxidised at the anode.

Organic structure analysis and identification

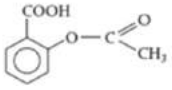
Mass spectrometry

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?



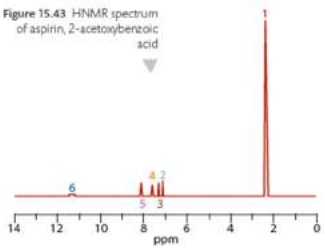
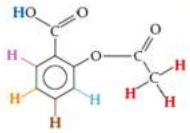
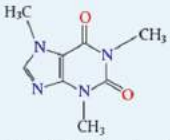


Figure 15.43 HNMR spectrum of aspirin, 2-acetoxybenzoic acid

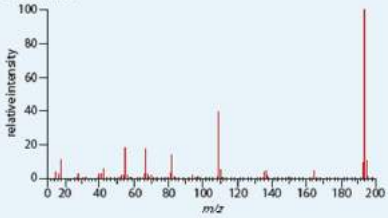


Peak	Chemical shift / ppm	Type of proton	Splitting pattern
1	2.3	3 equivalent protons on the $-CH_3$ group in the ester group	singlet
2	range 7–8	4 protons attached within the aromatic ring, each in slightly different chemical environments	doublet
3			triplet
4			triplet
5			doublet
6	11	–OH of carboxylic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

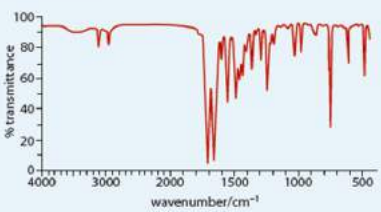
29 Caffeine has the following structure:



(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 sm
- Antibiotic resistance occurs when microorganisr

Applications and skills:

- Description of the environmental impact of med
- Discussion of environmental issues related to let
- 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 lll di

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.

- 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.