Medicinal chemistry and drug delivery

Scopes:

- the challenges of drug design - on identify, develop molecules and overcome problems
- the challenges of drug delivery on identify, design, develop materials and overcome problems.

Designing drugs

4 areas —— effective
'no' side-effect
specificity
cost / economical.

Effective and 'no' side-effect

When a molecule is to be used as a drug it is important that it is effective in achieving its desired effect and that undesirable side-effects are avoided.

Example: Thalidomide as sedative to pregnant mother in the early 1960s.

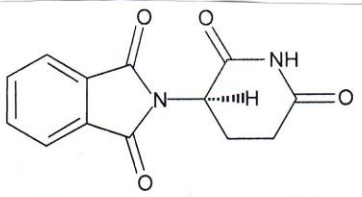
Valium (an alternative) was addictive.

The thalidomide produced was a mixture of two optical isomers.

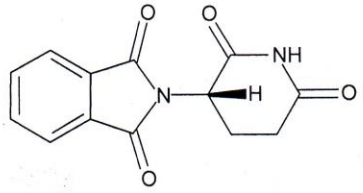
One of the isomers of thalidomide has disastrous side-effects.

It can cause babies to be born with congenital deformities such as shortened limbs.

The drug is said to be teratogenic



(R) – thalidomide desirable properties: sedative and antinausea drug



(S) – thalidomide teratogenic: causes birth defects

two enantiomers of thalidomide.

Nowadays, methods are available to chemists to design drugs and gain an understanding of ther action.

Understanding on the lock and key model enzyme catalysis and about competitive inhibition.

Drug molecules act by binding to receptors, and in many cases these receptors are enzymes.

Drugs can also be competitive inhibitors of enzymes and if a drug has optical isomers, only the isomer that is complementary to the shape of the enzyme active site will fit.

In order to bind to its receptor a drug must not only have the shape to fit, but must also be able to interact with the groups on the receptor molecule by hydrogen bonds, ionic interactions or van der Waals forces.
Chemists are able to use computer simulations to model how their drugs will fit into the receptor site.
They can also search databases to see if their drug will interact with other enzymes to get an idea of possible side-effects.
These computational methods have proved very powerful both in designing new medicines and in understanding how drugs act.

Economical reasons / cost.

Another reason for only using one optical isomer is economics.

Where a synthetic route to a pharmaceutical produces two chiral molecules, chemists seek a route that produces only the active molecule that is desired.

This process is called asymmetric synthesis.

A key reason for this development is that when two chiral molecules are produced from a non-chiral starting material, they are normally produced in equal quantities, so half of the reactants are wasted.

Asymmetric synthesis saves on resources and costs

A successful example of asymmetric synthesis is in the treatment of Parkinson's disease.

This disease causes much suffering and is characterised by tremors in the hands and loss of balance.

L-dopa (the L enantiomer of dopa) can alleviate the symptons.

The L-dopa must be free of D-dopa.
D-dopa has many unpleasant side-effects.
Chemists now make pure L-dopa for use by patients, and it does not change to D-dopa in the body.

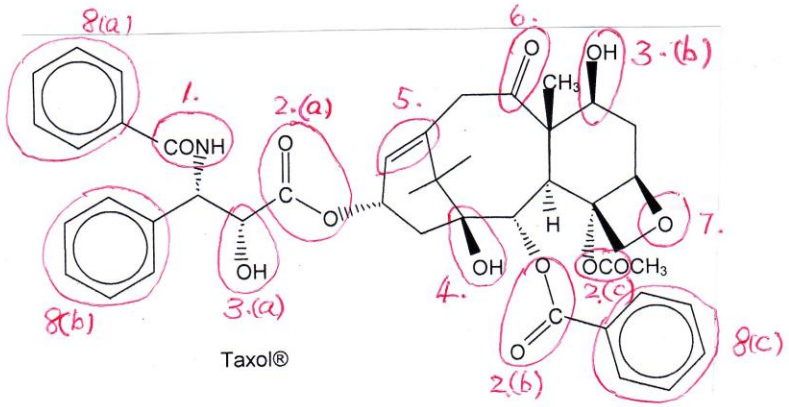
Improve efficacy.

When chemists are seeking a new pharmaceutical they may start from a natural product molecule that is known to have a positive effect.

Natural product molecule is molecule synthesised by a plant or other organism.

Example: anti-cancer drug Taxol® is a natural product found in yew trees.
It acts by binding to protein molecules in the cell and preventing the cell from dividing.
Only small amounts of Taxol® can be isolated from yew trees.
It became important to find ways of synthesising Taxol®.

Structure of Taxol®:



Taxol®

functional group:

1. – amide

2.(a),(b),(c) – ester

3.(a),(b) – 2° alcohol

4. – 3° alcohol

5. – alkene

6. – ketone.

7. – ether

8.(a),(b),(C) – benzene

Synthesising a molecule as large and complex as Taxol® is a major challenge and requires a sound knowledge of many different kinds of reactions.

Chemists first understand the structure of the Taxol® and then work out ways of making the drug.

The structures of such molecules can be worked out by the NMR and X-ray crystallography. techniques.

Chemists may also use techniques such as computer modelling in the process to plan the best route to take.

First success was achieved in 1994.

Research continues today as chemists are keen to minimise the number of reactions needed to make the synthesis more efficient in terms of cost and resources.

They are also keen to make similar molecules with slightly different shapes and functional groups in order to try and find a molecule that is even more effective and with fewer side-effects.

Exercise 1

Why are pure enantiomers rather than racemic mixtures the better option for use as pharmaceutical drugs from the point of view of:

i) a patient?

ii) a pharmaceutical company?

Workings

i) better compliance because
- less dosage required
- reduces risk of side-effects as the unwanted enantiomer might present a health hazard
- potentially more affordable

ii) • supplying safer drug – reduces the chances of litigation against the drug company as a result of side-effects caused by the unwanted enantiomer.
- possibly more affordable by bigger crowd of patients because may be cheaper as don't waste the unwanted enantiomer.

Exercise 2

Why are modern enzyme-based processes for manufacturing pure enantiomers more sustainable (environmentally friendly) than traditional synthetic routes used by the pharmaceutical industry?

Workings

- racemic mixtures produced in traditional synthetic routes
- this results in the need to seperate the mixture of enantiomers.
- this can use large volumes of organic solvent which have to be disposed of, along with the unwanted enantiomer.
- the process will also use more chemicals which require natural resources.
- enzymes are stereospecific.
- whole organisms can be used (without having to isolate enzymes)
- fewer steps in process resulting in more efficiency.