A4 - Pharmaceutical Aspects & Drug Development.

(a) To define shelf-life & outline factors that may influence drug potency during storage.

Shelf-life = period for which a minimum of 90% of the drug remains intact and available for delivery.

Factors influencing drug potency during storage

(1) drug instability - incessant, irreversible chemical reactions resulting in degradation products (ie. hydrolysis & oxidative reactions)

- most drugs are stable in the pH range 4-8 but those at more extremes ranges may undergo rapid decomposition.

- when drugs stored in powder or solid form -> decomposition more slowly.

- when H2O or saline added to as solvent -> accelerate the rate of decomposition.

(2) incompatibility - factors inherent in the drug itself & the environment

- temperature - higher temp can (i) increase the enzymatic metabolism of drugs -> decrease concentration (ii) lead to evaporation of solvents -> increase concentration

- photodegradation - Na+ nitroprusside, frusemide, vitamin A, halothane, catecholamines.

(3) maintenance of stertility -

(b) To describe methods of preserving shelf-life of drugs.

- goal = make a stable & appropriate formulation of a drug in which that active drug will be soluble & resistant to decomposition & contamination.

Decomposition

-> diminution of product potency because of reduction in the concentration of the active ingredient.

Mechanisms of decompositon & prevention:

(1) Hydrolysis

- chemical reaction with H2O
- most common form of drug degradation
- H+ + OH- -> hydrolytic cleavage
- culprits = lactam groups, ester or amide bonds

- ie. atropine, procaine, cocaine, phytostigmine, penicillins & cephalsporins.

- determine the pH at which drug is most stable and then add buffers to maintain it.
- alter the dielectric (polarity of drug) by addition of non-aqueous solvents such as glycerine & propylene glycol.
- solubilisation by surfactants
- modification of side-chain substituents
- lyophilisation (freeze-drying)

(2) Oxidation

- loss of electrons from a substance (addition of O2)
- at risk: vitamins, phenolic compounds (propofol) & catecholamines.

- remove O2 from pharmaceutical preparation
- addition of antioxidants
- addition of sulphurous acid salts (sulphur dioxide & sodium sulphite) -> aminoglcosides, catecholamines.

(3) Photochemical decomposition

- light + many drugs -> multistep degradation
- energy imparted increases as wave length increases -> UV light degration > than visible light

(4) other methods

- keep cool
- keep at a constant temperature
- keep in unopened packages
- do not expose to ambient pathogens
- use drugs with closer expiry dates first
- drugs stored in powder or solid form decomposes more slowly (limits hydrolysis on carboxylic acid, phoshate esters, amides, lactams & imines)
- ensuring no absorption occurs in container

Preservatives

= substances added to pharmaceutical products that prevent or inhibit the growth of microorganisms.
- almost all are weak acids with pKa = 4-5
- acidifying agents added so preservatives are unionised -> enter microbial cell walls.
- ie. benzalkonium chloride, chlorobutol and parabens.

(c) To describe the mechanisms of action & potential adverse effects of buffers, anti-oxidants, anti-mcirobial & solubilizing agents added to drugs.

Buffers

Mechanism

- weak bases or acids
- in unionized form -> increase absorption depending on its pKa & the pH of the absorbing tissue.
- buffers: $NaHCO_3$, phosphate, citrate, benzenesulphonic acid
- examples:

(1) Na+ carbonate added to thiopentone -> pH 11
(2) NaOH + propofol -> pH 7

Adverse effects

- thrombophlebitis
- preciptiation of salts

Anti-oxidants

Mechanism

- prevent oxidation by combining with free radicals
- reducing agents act by use of their low oxidation potential -> combine with O_2 leaving the active drug free from attack.

- examples:

(1) thymol in halothane
(2) ascorbic acid & sulphurous acid salts.

Adverse effects

- thymol -> cardiovascular depression, neurotoxicity, hypersensitivity reactions

Anti-microbial

Mechanism

- weak acids with pKa's of 4 to 5
- acidifying agents added so that agent is unionized -> can penetrate cell membrane of bugs.

- examples:

(1) benzyl alcohol - lorazepam
(2) chlorocresol
(3) phenol
(4) parahydroxbenzoic acid

Adverse effects

- may be a source of hypersensitivity reactions.

Solubilizing agents

Mechanism

(i) enhance solubility of poorly water soluble drugs.
(ii) because there is increase use of non-aqueous vehicles -> reduced rate of hydrolytic decomposition.

- examples:

(1) glycerol
(2) ethanol
(3) propylene glycol - low MW & water soluble, metabolised to pyruvate (in etomidate, GTN, diazepam)
(4) benzyl alcohol - 2% anti-microbial, 5% non-aqueous solvent.

Adverse effects

- irritant to veins
- preciptation
- propylene glycol - arrhythmia & hypotension when given quickly + also pain on injection.
- benzyl alcohol - dose related toxicity, hypotension.

(d) To outline the variation in generic nomenclature of commonly used drugs (eg.epinephrine/adrenaline, lidocaine/lignocaine).

BP	**USP**
Adrenaline	Epinephrine
Noradrenaline	Norepinephrine
Isoprenaline	Isoproterenol
Paracetamol	Acetaminophen
Lignocaine	Lidiocaine
Cinchocaine	Dibucaine
Thiopentone	Thiopental
Pethidine	Merperidine
Salbutamol	Albuterol
Amethocaine	Tetracaine

(e) To define isomerisation & provide a classification with examples. To describe the clinical importance of isomerism.

See diagram & definitions - isomers

Isomerism = existence of two or more ions/compounds that have the same atomic composition but different structural arrangement (& often have different pharmacological properties)

Two types

(1) Structural isomers = compounds with same molecular formula but different chemical structures (atoms arranged differently)

Tautomerism (dynamic isomerism) - two structural isomers existing in equilibrium.

(example: thiopentone - Na+ thiopentone is an alkaline solution (pH 11) & highly water soluble -> on injection in plasma (pH 7.4) drug becomes unstable & undergoes dynamic isomerism (H+ moves from S at position 2 -> N at position 3) -> less ionized, lipid soluble, BBB crossing form.

(2) Stereoisomers = compounds with same molecular formulae and chemical structure, but have different spatial orientation.

Enantiomers - compounds with mirror images that rotate a plane of polarised light left (left) or right (dextro). OR configuration of atoms around chiral atom from largest to smallest + rotates light right (R)

Diastereomers - not mirror images but have identical molecular formulae & chemical structure.

Examples in Anaesthesia

- 40% achiral, 60% chiral
- etomidate - R enantiomer
- ropivicaine - S enantiomer (enchanced vasoconstriction, prolonged duration, reduced motor block, reduced cardiotoxicity)
- thiopentone (R), methohexitone (S) - methohexitone is more potent & shorter half-life.
- ketamine (S) -> more potent & less psychotic emergence.

(f) To describe the processes by which new drugs are approved for research and clinical use in Australia, and outline the phases of human drug trials (phase I-IV).

Drugs = theraptic goods under the *Theraputic Goods Act 1989* & must be entered in the Australian Register of Theraputic Goods.

A clinical trial is an experiment conducted in humans in order to assess the effects, efficacy and/or safety of a drug or drug product.

In Australia the initiation of a clinical trial must go through (1) the clinical trial notification scheme or (2) clinical trial exemption scheme.

- trial must not violate the Statement on Ethical Conduct in Research involving Humans (1999) & the Voluntary Code of Conduct & pass through the indvidal institutional ethics committee.

Phase 0 - animal trials

- literature review
- animal studies for LD50

Phase I - basic PD & PK

- drug administered to a small number of volunteers (20-100)
- usually healthy (can be patients)
- determines: pharmacological activity, tolerance, absorption, distribution, metabolism & safety.
- need close monitoring
- identifies perfered routes of administration for subsequent trials.

Phase II - efficacy & safety

- 100's of patients suffering from the disorder.
- determines efficacy & safety
- several doses used to calculate theraputic range & maximum tolerated dose.

Phase III - clinical benefit in the disease states & acceptable incidence & nature of adverse effects.

- embarked upon when Phase II trials indicate that drug has a potential benefit which is greater than potential hazards
- extended clinical trials
- 1000's of patients
- multi-centre, randomised, double blind, placebo controlled.

Phase IV - safety amongst a large number of patients amongst the actual conditions of use