PHARMACEUTICAL ASPECTS AND DRUG DEVELOPMENT

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

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

(c) ***To describe the mechanisms of action and potential adverse effects of buffers, anti-oxidants, anti-microbial and solubilising agents added to drugs.***

(I) Overview of pharmaceutics:

"Pharmaceutics" → a branch of pharmacology that is concerned with manufacture and formulation of pharmaceutical products → it includes:

- (1) Packaging – Sterility, stability, ease of delivery, Etc.
- (2) Preparation (depends on route of administration)
    - Oral – palatable, dosage, solid vs syrup, enteric coated/slow release
    - Parental – solubility, stability, pain on IV
    - Transdermal – solubility, creamv vs ointments, occlusive dressing

> Note – "Bioequivalence" → 2 formulations of same drug are bioequivalent if the extent and rate of absorption are similar with no important differences in therapeutic or adverse effects

Drug additives → a part of "preparation" branch of pharmaceutics

- Functions:
    - (1) Preservative – Reduce rate of conversion of active ingredient into an inactive or toxic form, and reduce risk of contamination (Eg. bacterial, fungal)
    - (2) Enhance solubility of drug – ↑ dissolution of active drug in a deliverable aqueous form
- They should be – (i) chemically inert, (ii) non-toxic, (ii) devoid of pharmacological effect (including a lack of drug interactions)

(II) Overview of drug shelf life: Drug potency and Microbial contamination

> "Shelf-life" → the time (under appropriate storage conditions) that a drug maintains 90% of its activity and remains free of contamination

- (1) Drug potency decreases during storage 2° to decomposition → this occurs by:
    - (a) Hydrolysis
        - Most common mechanism affecting drugs presented in aqueous phase → H_2O is a reactive substance that produces free radicals/reactive species that hydrolyse drug bonds (esp amide, but also ester and lactam groups)
        - Prevented by reducing amount of drug in aqueous phase
    - (b) Oxidation
        - Involves loss of electrons → affects vitamins, catecholamines, phenolic compounds (Eg. propofol), adrenaline, aminoglycosides
        - Prevented by (i) removing O_2 (difficult to achieve as trace O_2 still causes [O]), (ii) adding antioxidants (true antioxidants (Eg. thymol), reducing agents (Eg. ascorbic aids, metabisulphite)), (iii) adding anti-oxidant synergists (Eg. promote activity of other anti-oxidants)
    - (c) Isomerism
        - Prevented by (i) maintaining temperature stability, (ii) storing drug away from light, (iii) using solvents
    - (d) Photochemical decomposition

        - Prevented by (i) using dark amber coloured bottles or ampoules, or (ii) storing drug away from light

> Note – Rate of drug breakdown (via aforementioned mechanisms) and drug potency with storage are affected by following factors:
> - (i) Temperature
> - (ii) pH
> - (iii) Oxygen
> - (iv) Light
> - (v) Humidity
> - (vi) Packaging
> - (vii) Additives/solvents

- (2) <u>Microbial contamination</u> of drugs during storage is minimised by:
    - (a) Sterile preparation and storage
    - (b) Heat sterilisation
    - (c) Antimicrobial preservatives:
        - Added to prevent or inhibit microbial growth that may have been introduced during manufacture
        - Include:
            - (i) Parabens (esters of PABA) → issues with skin reactions/allergy
            - (ii) Phenol
            - (iii) Benzyl alcohol → acts as both a preservative and solvent
            - (iv) Salts (Eg. Na metabisulphite)
            - (v) Benzalkonium chloride → issues with bronchoconstriction

(III) <u>Enhancing drug solubility</u>:

Several anaesthetic agents are poorly water soluble (due to their high lipid solubility) → dissolution in solution occurs by ↑ their solubility via:

- (1) Use of selected drug "salts" (Eg. sodium thiopentone, ketamine HCl, atracurium besylate, vecuronium bromide, adrenaline sulphate)
- (2) Alteration of molecular structure (Eg. prodrug methyl-dopate → methyldopa in vivo)
- (3) Choosing an appropriate solvent:
    - (a) Water – Universal solvent that is non-toxic, tasteless and inert, BUT main issue with drug decomposition 2° to hydrolysis
    - (b) Non-aqueous solvent (Eg. propylene glycol, benzyl alcohol) – Solubilises agents that are insoluble in H_2O; also reduces decomposition 2° to hydrolysis

> Important to note:
> - Propylene glycol – Mild antimicrobial effect; causes hypotension and painful IV injection
> - Benzyl alcohol – Antimicrobial effect at < 2%; non-aqueous solvent at > 5%

- (4) If solubility really poor:
    - (a) Co-solvent, such as mannitol (Ie. dantrolene, paracetamol IV)
    - (b) Emulsions
        - Defined as a pair of immiscible liquids, one dispersed as droplets throughout the other → can be either "oil-in-water" (o/w) or "water-in-oil" (w/o), depending on proportion of immiscible liquids
        - They are inherently unstable and tend to coalesce → thus, "Emulsifying agents" are added to ↑ stability and maintain droplets in a dispersed phase

Note – Types of "emulsifying agents":
- (i) Surfactant
- (ii) Cremaphor EL (used in propofol previously; vitamin K) → issues with hypersensitivity, complement activation, histamine release
- (iii) Soyabean oil/egg yolk phosphatide (used in propofol, diazepam)

    - Emulsion preparations have issues:
        - (i) Sensitive to changes in temperature and pH
        - (ii) Sensitive to added molecules
        - (iii) Aqueous phase prone to contamination (thus, contain water-soluble preservative)
        - (iv) Oil phase prone to rancidity (thus, contain antioxidant)
- (c) Lyophilisation (aka. freeze drying)
- (d) Adjusting pH of solution – ↑ fraction of ionised (or water-soluble) drug in accordance to its pKa by adding either acids (HCl) or bases (NaOH) to solution

Aside: Midazolam – Imidazole ring opening is pH-dependent:
- (i) Ring is open (polar and ionised) at pH 4-5 → water-soluble
- (ii) Ring is closed (non-polar and unionised) → lipid-soluble and pharmacologically active

(IV) <u>Others</u>:

<u>Alteration of pH of solution</u>:
- Reasons:
    - (1) To alter solubility of active drug (Eg. midazolam – see above)
    - (2) To alter onset/offset of drugs (Eg. LA have faster onset when % unionised is ↑ (Ie. adding of $NaHCO_3$ to ↑ alkalinity))
    - (3) To maintain stability (Eg. atracurium is degraded by Hofmann pathway)
- pH is altered by adding either – (i) Acid (Eg. HCl) or (ii) Base (Eg. NaOH, $NaHCO_3$)

<u>Maintaining isotonicity of solution</u>:
- Reasons:
    - (1) Reduce pain on injection
    - (2) Reduce thrombophlebitis
    - (3) Reduce haemolysis
- Isotonicity is maintained by addition of NaCl, mannitol or glycerol

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

There are 3 types of drug nomenclature:

- (1) Chemical – as designated by IUPAC (Eg. N-diethylaminoacetyl-2,6-xylidine hydrochloride)
- (2) Approved – as accepted by pharmacopoiae (Eg. lignocaine, lidocaine)

> Important to note – Pharmacopoiae:
> - Lists approved drugs and names (Eg. adrenaline/epinephrine, lignocaine/lidocaine)
> - Gives standards of production/manufacture and guarantees they have been met (Eg. B.P., U.S.P., Etc.)
> - Defines activity of drug (Ie. insulin, heparin)

- (3) Trade – as designated by drug company for "advertising" purposes, often related to approved name and hinting to drug activity (Eg. Xylocaine)

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

"Isomer" → molecules having the same chemical formulae but different structural arrangements

There are two types of isomers:

- (1) Structural isomer
  - Defined as molecules having the same chemical formulae but different order or arrangement of atomic bonds
  - Eg. Isoflurane vs enflurane, prednisolone vs aldosterone

> Note – "Tautomers":
> - Type of structural isomer → dynamic interchange b/t 2 forms of molecular structure a/w simple movement of electrons, often precipitated by a change in physical environment
> - Eg. STP (keto vs enol); midazolam (open ionised ring at pH 4; closed unionised ring at pH 7.4)

- (2) Stereoisomer
  - Defined as molecules having the same chemical formula and bond structure, but different spatial arrangements
  - Two subtypes:
    - (a) Geometric isomer
      - Molecule has dissimilar groups attached to two C-atoms linked either by a double bond or ring structure, such that free rotation of the groups is restricted → these groups are fixed to same side ("cis") or opposite side ("trans") of double bond or ring structure
      - Eg. Cis-atracurium, mivacurium
    - (b) Optical isomer
      - Molecule has one or more "chiral centre" (a carbon molecule with 4 different groups attached to it) → possess optical activity (Ie. rotate plane, polarised light) and may or may not mirror images of each other

> Note – Optical isomers are identified by:
> - (i) Rotation of plane, polarised light → d/l or +/-
> - (ii) Fisher convention → D/L (as relating to the configuration of groups on chiral atom)
> - (iii) Cahn-Ingold-Prelog → R/S (as relating to clockwise/counter-clockwise arrangement of atomic number of groups on chiral atom in ascending order)
>
> Important to note → these identification systems are NOT inter-related (Ie. R classification may be l or d to rotation of polarised light)

      - Two types:
        - (i) Enantiomers – Molecules with a single chiral centre (Ie. R and S isomers) that are mirrors images of each other (Eg. R/S-bupivacaine)
        - (ii) Diastereomers – Molecules with > 1 chiral centre presents with multiple possible stereoisomers, such that not all are mirror images of each other (Eg. atracurium has 4 chiral centres with 10 isomers)

Clinical significance of isomerism:

- There are types of isomeric preparations:
    - (1) Racemic mixture:
        - Mixtures of different enantiomers in equal proportions (Eg. Volatiles (except sevoflurane), bupivacaine, atropine, Etc.)
        - Note – The contributing pharmacokinetic/pharmacodynamic effects for each enantiomer may vary (Ie. one may be toxic; other may be therapeutic) despite their equal proportions
    - (2) Enantiopure preparation:
        - Preparation that selects a single isomer from a racemic mixture (Eg. S-ropivacaine and S-bupivacaine, S-ketamine, Dexmedetomidine, Etc.)
        - Note – There are advantages in selecting a single isomer from a racemic mixture (Ie. less toxicity, more therapeutic effect)
- Isomers can have different:
    - (i) Pharmacodynamic effects (therapeutic vs toxic)
    - (ii) Drug-receptor interactions → 3D structure determines molecular level interactions
    - (iii) Pharmacokinetics → esp metabolism due to drug-enzyme interactions
    - (iv) Physicochemical properties → enantiomers generally have same properties but other forms may have different properties

Examples:

- Levobupivacaine and ropivacaine – S-isomer is more active and less cardiotoxic b/c it binds VG Na^+ channel less favourably and unbinds it faster
- Ketamine – S-isomer more potent and is cleared faster
- Tramadol – (+) enantiomer is more effective as u-agonist/5-HT antagonist; (-) enantiomer inhibits NAd reuptake/promotes NAd release → racemic mixture is superior to enantiopure preparation as isomers act synergistically!
- Methadone – R (or l) isomer is an opioid; S (or d) isomer is a NMDA antagonist
- Morphine – (-) enantiomer is analgesically active (cf. (+) enantiomer)

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

Pre-clinical trials → experiments are done on animals

Clinical trials → experiments done on humans

- Phase one
  - Drug is tested in small group (n = 20-100) → evaluate safety, dosage and side-effects
- Phase two
  - Drug is given to a larger group → check efficacy and incidence of side-effects
  - Trials takes months-years
- Phase three
  - Drug is given to an even larger group (n > 1000) → confirm effectiveness and compare to current treatments
  - Trials are randomised and blinded → takes years
- Phase four
  - Drug is released into the general population → involves post-marketing surveillance, assessment of long-term effectiveness, and evaluation in specific groups (Eg. elderly)