MODULE 1: Preformulation Studies

Lecture 3

DISCLAIMER

All the content material provided here is only for teaching purpose

pKa Determination

- Dissociation constant is capability of drug to ionize within pH range of 1 to 10
- Solubility & absorption altered
- Henderson-Hasselbalch equation

$$pH = pKa + \log \frac{[\text{ionized drug}]}{[\text{unionized drug}]}$$

- Acidic compounds

$$pH = pKa + \log \frac{[\text{unionized drug}]}{[\text{ionized drug}]}$$

Weakly acidic drug pka is less than 3, unionized form in the stomach , Drug is ionized predominantly in intestine.

Basic drug pka=8-10, ionized form predominantly in stomach & intestine

pKa Determination

- **Determination pKa**
  - Analytical methods

  Determination of spectral shifts by UV or Visible spectroscopy (Dilute aq. Solution can be analyzed directly)

  Potentiometric Titration

  (pKa range of 3-10)

Factors affecting pKa

- Buffer
- Temperature
- Ionic Strength
- Co-solvent

Effect of Temperature

- Solution Process
- Endothermic
  - Heat of solution is positive
- Exothermic
  - Heat of solution is negative (lithium salts)

- Non-electrolytes &ionized forms ΔH between 4 to 8 kcal/mol
- Salt forms of drugs -2 to 2 kcal/mole (less sensitive to temp.)

- Effect solution dosage form design &storage condition.
- Solvent systems including co-solvents.
- Micelles
- Complexation

Partition Coefficient

- Ratio of unionized drug distributed between the organic & inorganic aqueous phase at equilibrium. System used are Octanol/water and Chloroform

$$P_{o/w} = \left(\frac{C_{oil}}{C_{Water}} \right)_{equilibrium}$$

Applications

Screening for biological activity

Drug delivery

/water

Dissolution

- Dissolution is expressed in terms of a rate process.
- Greater the rate, faster the dissolution.
- ***DISSOLUTION TESTING CONDITIONS GOVERNED BY***

Noyes-Whitney's equation is useful for estimating the rate of dissolution.

$$dC / dt = DA/ hV (C_s - C)$$

Apparatus

Dissolution Medium

Agitation

Validation

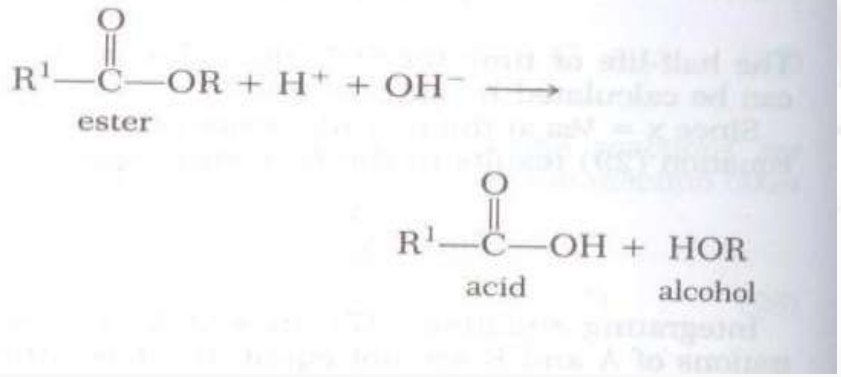
Degradation

Hydrolysis: interact with water molecule to yield breakdown product.

- Susceptible to the hydrolytic process: esters, substituted amides, lactones, and lactams.
- Eg: Anestheics, antibiotics , vitamins and barbiturates
- 1. Ester hydrolysis:

Ester hydrolysed into Acid + Alcohol

Acid or alkali catalysed hydrolysis



Factors to be considered in Hydrolysis

- pH
- Type of solvent : solvent lower dielectric constant
  - Eg.: ethanol,glycols, mannitol etc.
- Complexation : steric or polar effects. Eg.: caffeine with benzocaine – electronic influence of complexing agent – alters affinity
- Surfactants: nonionic , cationic , anionic stabilizes drug against base catalysis. Eg: 5% SLS – 18folds increase in t1/2 of benzocaine
- Modification of chemical structure
- Salts and esters

Oxidation - reduction

Second most common way.

Eg.: vitamins ,antibiotics etc

Mediated by free radicals or by molecular oxygen

Sensitive towards trace metal and other impurities

Redox reactions involve either transfer of oxygen or hydrogen atoms or transfer of electrons

Oxidation - reduction

Oxidation – presence of oxygen generates free radicals

These radicals propagate the oxidation reaction , which proceeds until inhibitors destroy the radicals or until side reactions eventually break the chain

Eg. Dopamine

Photolysis

- Photochemical
- Photosensitizer
- UV- violet portions – more active (shortet wavelength ,more energy)

Racemizationn

- Racemization – compound changes optical activity without changing the chemical composition.
- Levo and dextro form
  - Eg: l-adrenaline is 15-20times more active than dextro form
  - Racemic mixture
- Effects: Stability and therapeutic activity

References

- Lachman L Lieberman H.A, Kanig J.L, The Theory and Practice of Industrial Pharmacy, 3rd edition
- Michael E.Aulton. Pharmaceutics, The science of Dosage form design.
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