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pKa/Dissociation Constants

- Measure of ionization or dissociation extent.
- Highly dependant on pH of the medium.
- Important for:
  - Formulation
  - Pharmacokinetics
- In formulation: often the vehicle is adjusted to a certain pH to obtain a certain level of ionization of the drug for solubility and stability.
- In the pharmacokinetics: the extent of it strongly effects on drug's extent of absorption, distribution, and elimination.

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pKa/Dissociation Constants

Can be calculated by Henderson Hasselbach equation-

For acidic drugs…. pH= pKa + log [I]/[UI]

For basic drugs….pH= pKa + log [UI]/[I]

Where : UI = unionized drug
and I = ionized drug

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pH Solubility Profile

- **The solubility of acidic or basic drug will show difference in solubility with changes in pH.**

- **pH solubility profile of a drug can be established by running the equilibrium solubility experiment within specific pH range.**

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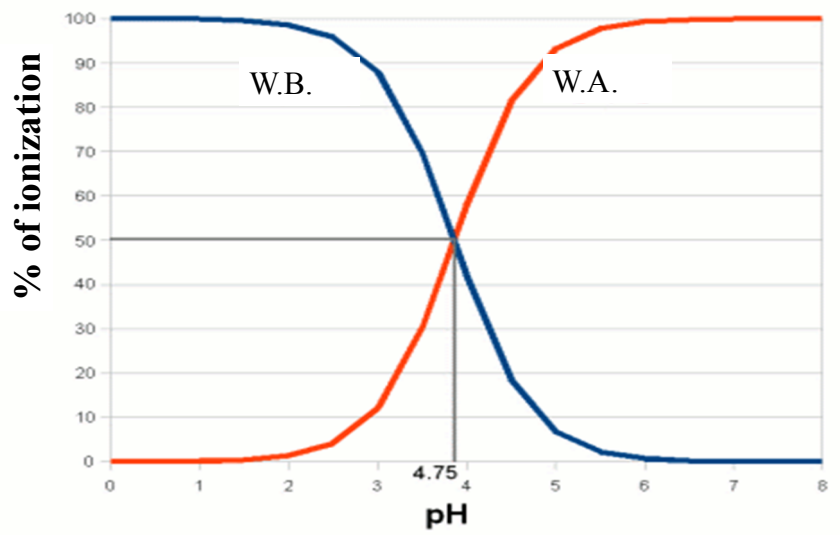

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Hydrates

- **Hygroscopic powders** are those that will tend to absorb moisture from the air.
- **Deliquescent powders** are those that will absorb moisture from the air and even liquefy.
- **Efflorescent powders** are those that may give up their water of crystallization and may even become damp and pasty.
- If a hygroscopic or deliquescent powder is being weighed on a balance, the powder may absorb moisture from the air and weigh heavier than it should.
- Solvates and hydrates must be packaged in "**tight**" containers to prevent the loss or gain of moisture.

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Organic Salt considerations

- **Sodium salicylate**
- **Ephedrine hydrochloride**
- **Codeine phosphate**

- These salts will affect:
  - Solubility
  - Stability
  - Dose
  - Easier to handle and manipulate production.

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Organic Ester considerations

- An ester is a compound of the general formula **R-C-O-R1** where R and R1 may be the same or different and may be either aliphatic or aromatic.
- Some drugs are esters by virtue of their internal chemical structure: **atropine**, **cocaine**, many local anesthetics.
- Some drugs are prepared as ester by the addition of other moiety eg: **cortisone acetate**.
- Adv: solubility, stability, resistance to degradation after administration, use as prodrugs.

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Organic Ester considerations

Some drugs are very soluble but tend to degrade rapidly when in solution. One approach to increase their stability is to prepare **esters** that are **poorly soluble**. This results in a "**suspension**" dosage form in place of a "solution" dosage form. A drug in a suspension dosage form degrades at a much slower rate than one in solution. After oral administration, the ester is cleaved and the active drug moiety released for absorption.

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Organic Ester considerations

Some drugs may cause **pain** at the site of injection, especially if they precipitate and damage the surrounding tissue. This can be overcome by preparing a drug with increased solubility. **Chloramphenicol** has low water solubility, but the succinate ester is formed to increase the water solubility of the drug and facilitate parenteral administration. This succinate ester is inactive but is hydrolyzed to release the active chloramphenicol moiety.

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Organic Ester considerations

- Esters are an important means of preparing **prodrugs** due to the number of **esterases** present in various parts of the body that will cleave the ester linkage, releasing the active moiety.
- Carboxylic acid esters are common in pharmacy and are neutral liquids or solids, which can be hydrolyzed slowly by water and rapidly by acids or alkalis into their components. Some of the simple esters are soluble in water, but those with more than four carbon atoms are practically insoluble in water.

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