### **INTRODUCTION:**

### The preformulation studies we should know the properties of the drug, potency relative to the competitive products and the dosage form, literature search providing stability and decay data, the proposed route of drug administration, literature search regarding the formulation approaches, bioavailability, drug release and pharmacokinetics of chemically related drugs. It also includes preliminary investigations and molecular optimization by the drug should be tested to determine the magnitude of each Suspected problem area (Step I), if a deficiency is detected, a molecular modification should be done (Step II). To overcome this deficiency molecular modification is done be salts, prodrugs, solvates, polymorphs or even new analogues.

### The influence of polymorphism on physicochemical characteristics of solid drugs such as powder property, melting point, and enthalpy of fusion, dissolution behavior and stability are discussed in detail. Furthermore, a variety of differences in drug bioavailability and curative effect of polymorphs are also summarized and discussed. This has led to the increased attention being given to the physical properties of solids that contain a dosage form.

**Physicochemical Properties:**

The ability of a chemical compound to elicit a pharmacological/therapeutic effect is related to the influence of various physical and chemical (physicochemical) properties of the chemical substance on the bio molecule that it interacts.

a.    Investigation of physical and chemical properties of a drug substance – alone and or when combined with excipients is crucial during pre-formulation studies.

b.    The development of any dosage form new drug, it is essential that certain fundamental physical and chemical properties of drug powder are determined.

c.    This information may dictate many of subsequent event   and approaches in formulation development.

d.    The physicochemical properties are the first step in the rational development of a dosage form of a drug substance alone and when combined with excipients.

The ability of a chemical compound to elicit a pharmacological/ therapeutic effect is related to the influence of various physical and chemical (physicochemical) properties of the chemical substance on the bio molecule that it interacts with.

1. Physical Properties Physical property of drug is responsible for its action
2. Chemical Properties The drug react extracellularly according to simple chemical reactions like neutralization, chelation, oxidation etc.

**Various Physico-Chemical Properties are:**

Solubility 

Partition Coefficient 

Dissociation constant 

Hydrogen Bonding 

Ionization of Drug 

Redox Potential 

Complexation 

Surface activity 

Protein binding 

Isosterism

1. **Solubility**:

• The solubility of a substance at a given temperature is defined as the concentration of the dissolved solute, which is in equillibrium with the solid solute.

• Solubility depends on the nature of solute and solvent as well as temperature , pH & pressure.

• The solubility of drug may be expressed in terms of its affinity/philicity or repulsion/phobicity for either an aqueous or organic solvent. 

The atoms and molecules of all organic substances are held together by various types of bonds (e.g. hydrogen bond, dipole –dipole, ionic bond etc.) These forces are involved in solubility because it is the solvent- solvent, solute-solute, solvent-solute interactions that governs solubility.

**Methods to improve solubility of drugs**

1. Structural modification (alter the structure of molecules)
2. Use of Cosolvents (Ethanol, sorbitol,PPG,PEG)
3. Employing surfactants
4. Complexation 

**Importance of solubility**:

1. Solubility concept is important to pharmacist because it govern the preparation of liquid dosage form and the drug must be in solution before it is absorbed by the body to produce the biological activity.
2. Drug must be in solution form to interact with receptors.

**Dissolution:**

Dissolution is a process in which a solid substance solubilises in a given solvent i.e. mass transfer from the solid surface to the liquid phase. The dissolution rate is a measure of the actual release rate of the compound at the given particle size etc. in an aqueous media. Dissolution is a process by which a solid substance (drug) goes into the solution, that is, mass transfer of molecules from the solid surface to the liquid phase [7]. It often varies considerably with solid form, e.g. Particle size and shape Dissolution tests are used for:

 Ensuring that production processes are under control.

**USP Dissolution Apparatus:**

1)   Apparatus 1 - Basket (370C)

2)   Apparatus 2 - Paddle (370C)

3)   Apparatus 3 - Reciprocating Cylinder (370C)

4)   Apparatus 4 – Flow-Through Cell (370C)

5)   Apparatus 5 – Paddle over Disk (320C),

6)   Apparatus 6, Cylinder (320C),

7)   Apparatus 7, Reciprocating Holder

1) Apparatus 1 - Basket (370C)- It comprises of borosilicate glass and holds a capasity of up to 1000ml. The shape is semi-hemespherical at the bottom while its shaft is made out of stainless stell.The shaft hold the cylinder basket it is usually refered to as rotating basket because it rotates smoothly and its rotating speed must be in form with the recommended USP the common speed limit is 100 rpm.It is used for capsules or tablet, suppositories,floating dosage form and delayed release.

2) Apparatus 2 - Paddle (370C)- This apparatues specially made and it commes with a coated paddle that reduces the disturbance from the stirring apparently,it as a blade that comes in contact with the bottom of the shaft.the paddle apparatues is designed from stainless steel.it also has a platinum wire that protects the capsules from floatin.The paddle motor speed is usuallly at 40 and the paddle kept add at 37c.The paddle is kept in the position that specified in the current USP.It has a motor speed of 50rpm for capsule while 25rpm for suspension.

3) Apparatus 3 - Reciprocating Cylinder (370c)- This dissolution apparatus is usually considered in a product development for controlled release prepration. The reasone for this is aid the release of product in GI tracts by exposing them to various physicochemical conditions and mechanical conditions.it is an a easy method for a drug testing and it does not pose any problem with the PH values of its solution.It is used for extended release,chewable tablets.

4)  Apparatus 4 – Flow-Through Cell (370c)- It is a made of two types which are the open system and the closed system.The open system has a fresh medium pumped through the cells and then the fractions received. The fraction are usually drawn every 30min.The dissolution test conducted with this apparatus should be conducted in the best sink condition available.The closed system on the other hand is where the medium is pumped into the circle but not replaced by a fresh medium.It is a normally used for drugs with a low dosage and a test is conducted in small volumes.The flow through the cell apparatus is designed like a reservoir and is a commonly used  for implants.

5) Apparatus 5 – Paddle over Disk (320c)- Transdermal Delivery System, use paddle and vessel from Apparatus 2 with a stainless steel  disk assembly to hold the transdermal on the bottom of vessel.

6) Apparatus 6, Cylinder (320c)- Transdermal Delivery System, use Apparatus 1 except replace the basket shaft with a stainless steel cylinder element.

7) Apparatus 7, Reciprocating Holde-or transdermal delivery systems and also a variety of dosage forms

 Factor affecting dissolution process-

1    Factor relating to the physicochemical properties of drug

2    Factor related to drug product formulations

3    Factor related to the dissolution testing device centricity of agitating (stirring) element

4    Factors related to dissolution test parameters

5    Miscellaneous Factor.

**Partition Co-efficient:**

Drug (aqueous) PC Drug (lipid) 

Partition co-efficient is one of the Physicochemical parameter which influencing the drug transport & drug distribution., the way in which the drug reaches the site of action from the site of application. 

Partition co-efficient is defined as equilibrium constant of drug concentration for unionized molecule in two phases. 

P[Unionizedmolecule] = [drug]lipid / [drug]water

For ionized (acids, bases and salts)

P[Ionized molecule] = [drug]lipid

1. a ][drug]water

a = degree of ionization in aqueous solution. 

Partition coefficient affects the drug transfer characteristics. The contribution of each functional group & structural arrangement help to determine the lipophilic or hydrophilic character of drug molecules. 

It is widely used in QSAR.

Factors affecting Partition Co-efficient:

*  pH
*  Co solvents
*  Surfactant
*  Complexation

Partition Co-efficient are difficult to measure in living system. They are usually determined in vitro 1-octanol as a lipid phase and phosphate buffer of pH 7.4 as the aqueous phase. 

1. octanol as a lipid phase because, 
2. It has polar and nonpolar region 
3. Po/w is easy to measure 
4. Po/w often correlates with many biological properties 
5. It can be predicted using computational mode

The Partition co-efficient, P is dimensionless and its logarithm,

log P is widely used as the measure of lipophilicity.

• The log P is measured by the following methods:

1. Shake flask method
2. Chromatographic method (HPLC) •

Phenobarbitone has a high lipid/water partition coefficient of 5.9.

Thiopentone sodium has a chloroform/water partition coefficient of about 100, so it is highly soluble in lipid. •

Hence, thiopentone sodium is used as ultra-short acting barbiturates.

**What else does lopP affects?:**

* Binding to enzymes /receptor
* Aqueous solubility
* Binding to P450 metabolising enzymes
* Absorbance through membrane
* Binding to blood/tissue proteins

**Importance of partician coefficient :**

* It is generally used in combination with the Pka to predict the distribution of drug in biological system. 
* The factor such as absorption, excretion & penetration of the CNS may be related to the log P value of drug. 
* The drug should be designed with the lowest possible 
* Log P, to reduce toxicity, nonspecific binding & bioavailability

Dissociation constant: 

**Hydrogen Bonding** :

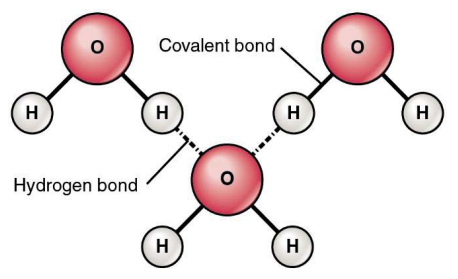
Hydrogen bond is a strong type of dipole-dipole interaction that occurs between a molecule containing a hydrogen atom and a strongly electronegative atom such as fluorine, oxygen, or nitrogen.

In order to create the bond, the hydrogen atom must be covalently attached to another electronegative atom.



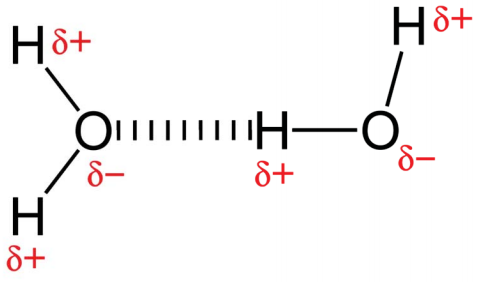
A perfect example of hydrogen bond is water.

Hydrogen bonds can also exist between alcohol molecules, carboxylic acids, aldehydes, esters, and polypeptides.



In a water molecule, the hydrogen lone electron is pulled by the covalently attached oxygen atom, creating a naked nucleus on the side of the hydrogen atom facing away (partial positive charge).

This side of the hydrogen atom can get close to neighboring oxygen atom (with a partial negative charge) and interact strongly with it.



Hydrogen bonds are responsible for many unusual physical properties of water including its abnormally low vapor pressure, high boiling point, and the greater volume of ice water.

Hydrogen bonding is stronger than all Van der Waals intermolecular forces (they are given their own classification), but are still weaker than ionic and

covalent bonds

**Pka / Ionization of Drug/ ionization constant:**

·      Most of the drugs are either weak acids or base and can exist in either

·      Ionised or unionized state.

·      The ionization of the drug depends on its pKa and pH.

·      The rate of drug absorption is directly proportional to the concentration of the drug at absorbable form but not the concentration of the drug at the absorption site.

·      E.g.: Aspirin in stomach will get readily absorbed because it is in the un-ionized form (99%).

·      E.g.; Barbituric acid is inactive because it is strong acid.

·      5, 5 disubstituted Barbituric acid has CNS depressant action because it is weak acid.

·      E.g.: Phenytoin injection must be adjusted to PH12 with Sodium Hydroxide to obtain 99.98% of the drug in ionised form.

·      Tropicamide eye drops, an anti cholinergic drug has a pka of 5.2 and the drug has to be buffered to pH 4 to obtain more than 90% ionization.

**Methods to determine pka:**

1)   Potential electric method

2)   Conductivity method

3)   Dissolution rate method

4)   Liquid-liquid partition method

**Solid state characteristics:**

The solid-phase characteristics of drugs, such as amorphicity and crystallinity, have been shown to have a significant effect on the dissolution rate. Studies have demonstrated that the amorphous form of a drug usually exhibits greater solubility and higher dissolution rate as compared to that exhibited by the crystalline form.

Polymorphism the polymorphic forms of drugs have shown to influence changes in the solubilizing characteristics and thus the dissolution rate of the drug substance. Numerous reports have shown that polymorphism and the states of hydration, salvation, and/or complexation markedly influence the dissolution characteristics of the drug.

Co-precipitation and complexation Numerous reports have shown that polymorphism and the states of hydration, salvation, and/or complaxation markedly influence the dissolution characteristics of the drug.

Radical characteristic according to Nernst--Brunner theory, the dissolution rate is directly proportional to the surface area of the drug. Since the surface area increases with decreasing particle size, higher dissolution rates may be achieved through the reduction of particle size. This effect has been highlighted by the superior dissolution rate observed after micronization of certain sparingly soluble drugs as opposed to the regularly milled form.

**CONCLUSION:**

The physicochemical property is most important factor in solid dosage form Coues it’s occurring or chances to difficulties in formulation. The quality and curative effect of solid drugs, polymorphism of drug substances has been investigated in the pharmaceutical field for over 50 years. BCS relies on black and white definitions of solubility and permeability, are these definitions reliable or realistic, and There may be a risk of misclassification. The study of preformulation, characterization is important in solid dosage form.