''बेटी बचाओ, बेटी पढ़ाओ''

JAYOTI VIDYAPEETH WOMEN'S UNIVERSITY, JAIPUR

FACULTY OF PHARMACEUTICAL SCIENCE

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Course : B.Pharm (V-Sem)

Session : Pre formulation Studies

(Industial Pharmacy – I)

Academic Day starts with –

- Greeting with saying **'Namaste'** by joining Hands together following by 2-3 Minutes Happy session, Celebrating birthday of any student of respective class and **National Anthem**

PREFORMULATION STUDIES

I. PHYSICAL CHARACTERISTICS

A. BULK CHARACTERISTIC

1) Particle Size & Surface Area.
2) Polymorphism.
3) Crystallinity.
4) Hygroscopicity.
5) Flow properties & Bulk density.
6) Compressibility.
7) Drug-Excipient Compactibility.
8) Electro static charge.

9) Osmolarity.

10) Rheology.

11) Wettability.

B. **SOLUBILITYANALYSIS**

1) Aqueous Solubility.
   a) Intrinsic Solubility.
   b) Dissociation Constant.
2) Solubilization.
3) Partition Coefficient.
4) Thermal effect.
5) Commonion effect.
6) Dissolution.

PREFORMULATION

It is defined as phase of research and development in which preformulation scientist characterize physical & chemical properties of new drug molecule in order to develop safe, effective, and stable dosage form.

DIRECT BENEFITS:

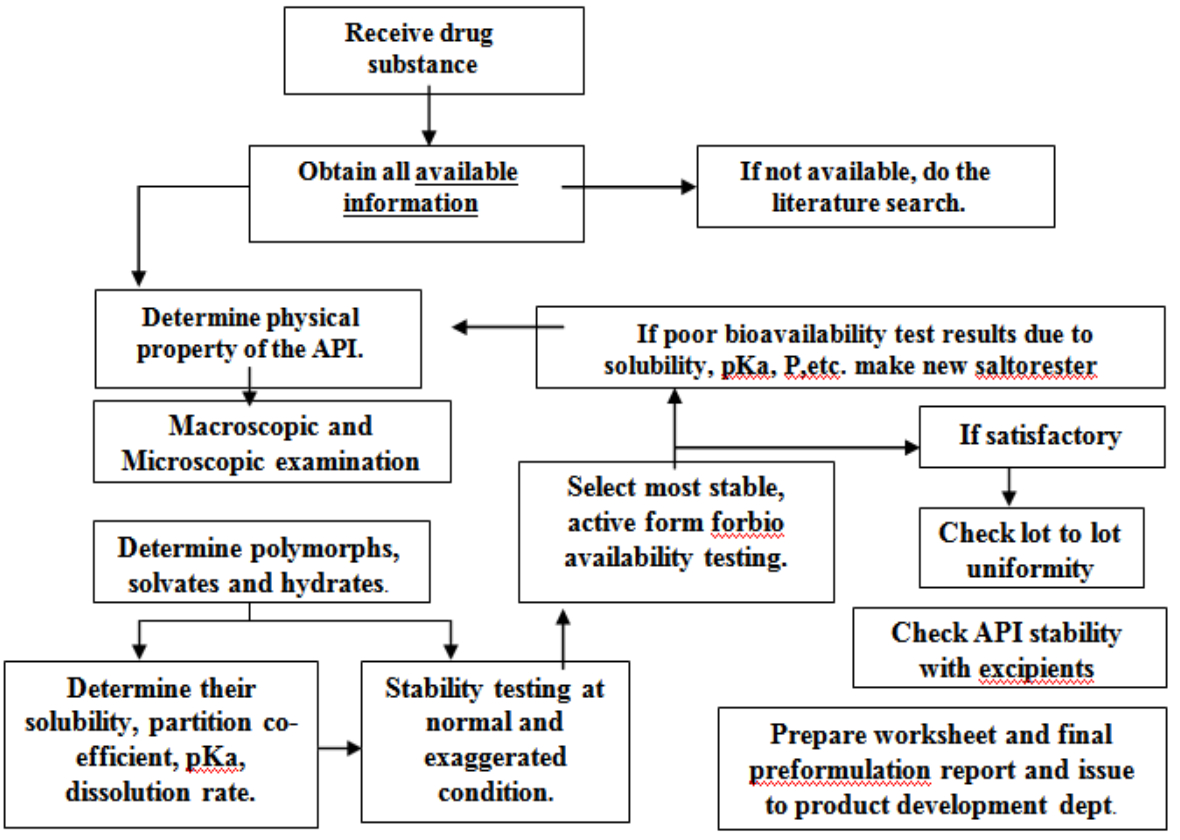
- Gives direction for development of formulation in choice of dosage form, excipients, composition, physical structure.
- Helps in adjustment of Pharmaco kinetics and bio pharmaceutical properties.
- Support for process development of drug substance (yield, filtration.).
- Produce necessary and useful data for development of analytical methods.

According to USFDA it can be characterized as:-

- Melting point (hot stage microscopy).
- IR spectroscopy.

- XRD.
- Thermal analytical technique.
- Solid state Raman spectroscopy.
- Crystal line index of refraction.
- Phase solution analysis.
- Solution calorimetery.
- Comparative intrinsicd is solution rate.

FLOW CHART FOR PRE FORMULATION STUDY :



[B] SOLUBILITY ANALYSIS

AQUEOUSSOLUBILITY

A drug must possess aqueous solubility for therapeutic efficacy in physiological pH range of 1 to 8 at 37ºC. Poor solubility (<10mg/ml) may

result into bio absorption problems. If solubility of drug is less than 1 mg/ml it indicates the need for a salt, particularly if the drug will be formulated as a tablet or capsule. In the range1-10mg/ml serious consideration should be given to salt formation.

There are **2 fundamental properties** mandatory for a new compd.

[a] Intrinsic Solubility (Co).

[b] Ionization Constant (pKa).

[a] INTRINSIC SOLUBILITY(Co):-

The solubility of weakly acidic & weakly basic drug as a function of pH can be predicted with the help of eqn.

$S = So \{1+(K_1/ [H^+])\}$ ---------- for weak acids.

$S = So \{1+([H^+]/ K_2)\}$ ---------- for weak bases.

where, S= Solubility at given pH.

So = Intrinsic solubility of the neutral form. K_1=Dissociation constant of weak acid.

K_2=Dissociation constant of weak base.

The in trinsic solubility should ideally be measured at 2 temperatures:

a) 4 ºC→To ensure physical & chemical stability.

b) 37ºC→To support bio pharmaceutical evaluation.

Method to determine solubility

(1) Equilibrium solubility method

(2) Turbido metric solubility method

(3) Nephlo metric solubility method

(4) Ultra filtration LC/MS solubility method

(5) Direct solubility method

(6) NRTL– SAC method

(7) COSMOSAC method

Solubility parameter is used to design dry suspension of cefaclor as a dual pack system. (IJPS):

BASED ON SOLUBILITY PARAMETER ONE CAN DECIDEWHETHER PARTICULAR SOLUTE WILLS OLUBILIZE INAGIVEN SOLVENT OR NOT. SOL. PARAMETER OF CEFACLOR VARIES GREATLY WITH WATER & CEFACLOR IS HIGHLY LIPOPHILIC SO IT IS INSOL. IN WATER WHEN WATER WAS MIXED WITH CO-SOLVENT PEG IN THERATIO 80:20 THE SOL. PARAMETER OF THE MIXTURE WAS FOUND SIMILAR TO THAT OF CEFACLOR & THEREFORE IT GETS EASILY SOLUBILIZEDINIT…

DUAL PACK SYSTEM IS PREFERRED BECAUSE CEFACLOR BEING A CEPHALOSPORIN CLASS ANTIBIOTICIS HIGHLY UNSTABLE IN WATER SO…

[b] IONIZATION CONSTANT (pKa):-

75% of all drugs are weak bases, 25% are weak acids and only,

5% are noni on i camphotericor alcohol.

The unionized forms are more lipid soluble & more rapid lyabs or bed from g.i.t.

The relative conc. of unionized & ionized form of weakly acidic or basic drug in a solution at a given pH can be calculated using the **Henderson-Hassel balch equation**:-

pH=pKa +log [unionized form]/[ionized form] ---------- for weak bases.

pH=pKa+log [ionized form]/ [unionized form] ---------- for weak acids**.**

Uses of these equations :-

1) To determine pka.
2) To predict solubility at any pH provided that Co&pKa are known.
3) To facilitate the selection of suitable salt forming compounds.
4) It predicts the solubility & pH properties of the salts.

Limitation:-

To fail outside the pH limits of 4-10 or when the solution is very dilute.

Method to determine pka:-

1) Potentio metric method.
2) Conductivity method.
3) Dissolution rate method.
4) Liquid-Liquid partition method.
5) Spectro photo metric method.

SOLUBILIZATION

Many different approaches have been developed to improve drug solubility:

1) **Micronization:-**

   Eg. Grise ofulvin shows increased solubility by reducing particle size.

2) **Change in pH:-**

   Eg. Solubility of Nime sulide increases as pH is increased. [**Chemical Abstracts, 133(6);August 2000:79182 g**]

   Eg. Arginine increases solubility of coumarins**. [Chemical Abstracts, April 2009;150:290306j]**

   Eg. Etopo side formulation is difficult because of its poor solubility & labile chemical stability so its most stable formulation is Etopo side loaded emulsion (ELE) atp H4-5.

   [**JPS July2007;96(7):1791**]

3) **Cosolvency:-**

- Addition of a water miscible solvent can often improve the solubility of a weak electro lyte or nonpolar compound in water by altering the polarity of the solvent.
- The choice of suitable cosolvent is limited for P'ceutical use because of possible toxicity & irritancy.
- Ideally suitable blends should possess values of dielectric constant between 25-80. Commonly used co solvent saree than ol, sorbitol, glycerin, propy lenegly col,
- dimethy lacetamide (DMA), DMSO, etc.

4) **Solubilization by surfactant:-**

- Eg. Gelucire 44/14 is a surface active excipient that can solubilize poorly soluble drugs. [**JPS June 2004;93(6):1471**]
- Eg. Anionic & cationic surfactants exhibited dramatically higher solubilization for gliclazide, while nonionic surfactants showed significantly lower solubilizing ability. [**JPS April 2003;92(6):839**]

5) **Complexation:-**

Eg. The Complexation of iodine with 10-15% poly vinyl pyroli done (PVP) can improve aqueo us solubility of active agent.

6) **Formation of Inclusion Compound:-**

- Eg. The aqueous solubility & chemical stability of Quercetin can be improved via Complexation with β-cyclodextrin.
- Eg. The enhancement of solubilization increased 300 fold for Nimodipine at a polymer conc. 10% by use of water solubled endrimer based on polygly cerol.
- Eg. Enhanced solubilty of oxicams through inclusion of β-cyclodextr in and its dvts.

7) **Chemical Modification:-**

Many poorly soluble drugs modified into salt form (water soluble).

8) **Use of Metastable polymorphs:-**

Eg. B form of Chlorampheni colpalmitate is more water soluble than A & C forms.

PARTITION COEFFICIENT :-

- water partition co efficient is commonly used.
    - P= (Conc. of drug in octanol) / (Conc. of drug in water)---For union iz able drugs.
    - P= (Conc. of drug in octanol) / (1-α)*(Conc. of drug in water) --- For ionizable drugs. where α=degree of ionization.
    - P >1□ Lipophilic drug.
    - P <1□ Hydrophilic drug.
    - The value of Pat which maximum activity of controlled release dosage forms is observed is approximately 1000 : 1inoctanol / water.

Methods to determine P:-

a) Shake Flask Method.
b) Chroma to graphic Method (TLC, HPLC).
c) Counter Current & Filter Probe method.

Applications of P:-

- Measure of Lipophilic character of molecules.
- Recovery of antibiotics from fermentation broth.
- Extraction of drug from biological fluid for therapeutic monitoring.
- Absorption of drug from dosage forms. (Ointments, Suppositories, Transdermal patches).

- Study of distribution of flavoring oil between oil & water in emulsion.

THERMAL EFFECT:-

- Effect of temperature on the solubility of drug can be determined by measuring heat of solution. (ΔHs).

ln S=-ΔHs/R*T+C.

where, S=Molar solubility at temperature T (ºK).

R=Gas constant.

- Heat of solution represents the heat released or absorbed when a mole of solute is dissolved in a large quantity of solvent.
- Mostly solution process is endo thermic (ΔHs=+ve) & thus increasing the solution temperature increase the drug solubility.
- Typical temp. range should include 5ºC, 25ºC, 37ºC & 50ºC.

Importance : Determination of temperature effect on solubility helps in predicting storage condition & dosage form designing.

COMMONION EFFECT:-

Addition of commonion reduces the solubility of slightly soluble electrolyte.

The "**salting out"** results from the removal of water molecules as solvent due to the competinghydration of otherions.

So weakly basic drug which are given as HCl salts have decreased solubility in acidic solution.

Eg.Chlortetracycline, Papaverine, Bromhexine, Triamterene, etc.

The reverse process "**salting in"** arises with larger anions. (Eg. Benzoate, salicy late) which can open the water structure.

These hydrotropes increase the solubility of poorly water soluble compounds.

To identify a common ion interaction the IDR (Intrinsic dissolution rate) of HCl salt should becompared between

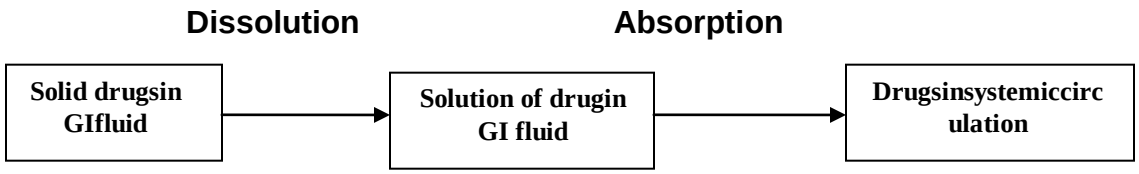
a) Water & water containing 1.2%W/VNaCl.

b) 0.05 M HCl & 0.9% NaClin 0.05 MHCl.

Boths a line media contains 0.2MCl⁻which is typically encountered influids in vivo.

DISSOLUTION

- The absorption of solid drugs administered or all y can be understood by following flow chart.



- In many instances, dissolution rate in the fluids at the absorption site is the rate limiting step in the absorption process.
- Dissolution rate can affect
  - On set of action.
  - Intensity of action.
  - Duration of response.
  - Control the overall Bio availability of drug form.
- Dissolution is to be considered of 2 types:

[1] Intrinsic dissolution

The dissolution rate of solid in its own solution is adequately described by **Noyes-Whitney equation:**

$$dC/dt = AD(Cs-C)/hv$$

where, dc/dt = Dissolution rate.

A = Surface area of dissolving solid.D =Diffusion coefficient.

C = Concentration of drug in solution.

h = Thickness of diffusion layer (at the solid- liquid interface). v=Volume of dissolution medium.

Cs=Solute concentration in the diffusion layer.

This equation helps to the pre formulation scientist in predicting if absorption would be dissolution rate limited or not.

Method to determine in trinsic dissolution:-Rotating disk method or Wood's apparatus:

This method allows for the determination of dissolution from constant surface area, obtained by compressing powder into a disc of known area with a die-punch apparatus.

[2] Particulate dissolution

This method determines the dissolution of solid sat different surface area.

A weighed amount of powder sample from a particular sieve fraction is introduced in the dissolution medium. Agitation is usually provided by a constant speed propeller.

It is used to study the influence on dissolution of particle size, surface area & mixing with excipients.

- **Next Topic-**
  - Continuation of pre formulation with other parameters

Academic Day ends with-

National song' Vande Mataram'