Module 01

Concept of Pre-formulation-

To develop stable, safe and effective dosage form, there must be study to collect basic information on the physical and chemical characteristics of the drug substance. These studies are known as preformulation.

Preformulation study include-

a. Identification of the drug and establishment of analytical methodology

b. Study of physical properties of the drug- Organoleptic properties, Physical Description, Particle Size and shape, Powder flow properties, Melting Point, Polymorphism, Solubility, Intrinsic solubility (C_o), Dissolution, Intrinsic dissolution rate, Partition coefficient (Log P), Wetting, Dielectric constant, pKa, Hygroscopicity

c. Study of chemical properties of the drug- Hydrolysis, Oxidation, drug stability, Polymerization, Isomerization, Racemization, Photolysis, Decarboxylation and Deamination

d. Study of interaction of drug with excipients

Identification of the drug and establishment of analytical methodology/ spectroscopy

The first step in preformulation is to establish a simple quantitative analytical method. Most drugs absorb light in ultraviolet wavelengths (190-390nm) since they are generally aromatic and may contain double bonds. Using UV spectrum of the drug, it is possible to choose an analytical wavelength (often the wavelength of maximum absorption, λ_{max}) suitable to quantify the amount of drug in particular solution.

Excitation of the molecule in solution causes a loss in light energy and the net change from the intensity of the incident light (I_o) and the transmitted light (I) can be measured. The amount of light absorbed by a solution of drug is proportional to the concentration (C) and the path length of the solution (l) through which the light has passed. Following equation is the Beer-Lambert Law where e is the molar extinction coefficient.

Absorbance (A) = $\log_{10}$ (I_0/I) = eCl

In pharmaceutical science, it is usual to use the specific absorption coefficient $E^{1\%}_{1cm}$ ($\mathbf{E^1_1}$) where the sample path length is 1 cm and the solution concentration is 1% w/v (10 mg/mL).

UV analysis is very simple and convenient quantitative technique that is suitable at this early stage of preformulation and some newer techniques like HPLC are used for assay of the drugs.

Organoleptic properties

Many drug substances are unpalatable and unattractive in their natural state and their dosage forms, particularly oral preparations may require the addition of approved flavors, perfumes and/or colors. Unpleasant taste can be overcome by using water-insoluble derivatives of drugs which have little or no taste. Examples are uses of chloramphenicol palmitate and amitriptyline pamoate but bioavailability must remain unchanged. If as insoluble derivative is unavailable or cannot be used, a flavor or perfume can be used. Colours are used to improve an existing drug color. Colours can be obtained from natural sources like carotenoids or synthesized like amaranth.

Physical Description

When a liquid drug is to be administered orally and solid dosage form is desired, one of two approaches is used. First, the liquid substance may be sealed in a soft gelatin capsule e.g. vitamins A, D, E and cyclosporine are available in capsule form.

Second, the liquid drug may be developed into a solid ester or salt from that will be suitable for tablets or drug capsules. For example, scopolamine hydrobromide is a solid salt of the liquid drug scopolamine and is an easily pressed into tablets. Another approach to formulate liquids into solids is by mixing the drug with a solid or melted semisolid material, such as a high-molecular-weight polyethylene glycol.

Particle Size and shape

During some processing procedures, the solid drug powders must flow freely and not become entangled. Spherical and oval powders flow more easily than needle-shaped powdered and make processing easier.

Particle size reduction results in an increase in the specific surface of powders. Poorly soluble drugs become more readily bioavailable when administer in a finely subdivided form with larger surface than as a coarse material. Examples include griseofulvin, phenothiazine, chloramphenicol, tolbutamide, indomethacin and spironolactone.

Sometimes fine powders (hydrophobic drugs) can also increase air adsorption or static change leading to wetting or agglomeration problems. Micronizing drug powders can lead to polymorphic and surface energy changes which cause reduced chemical stability.

Other dosage forms are also affected by particle size including suspensions (for controlling flow properties and particle interactions), inhalation aerosols (for optimal penetration of drug particles to absorbing mucosa) and topical formulations (for freedom from grittiness).

The Coulter Counter and laser light scattering are widely used for particle size analysis.

Powder flow properties- Flow characteristics are very important in handling of the drug powder during dosage form development. Flow properties can be evaluated by measurements of bulk density, tapped density and angle of repose.

Carr's Index- Carr's Index = [(Tapped density – Bulk density)/ Tapped density] x 100

Hausner Ratio = Tapped density/ Bulk density

A Hausner ratio of less than 1.25 (equivalent to 20% Carr) indicates good flow, while greater than 1.5 (equivalent to 33% Carr) indicates poor flow. A Hausner ratio between 1.25 and 1.5 glidants can be added to improve flow.

Angle of Repose- Angle of repose (θ) can be determined by fixed funnel method and can be calculated using formula: $\theta = \tan^{-1} h/r$

Where h is cone height, r is radius of heap

Table: Carr's index and Angle of repose as an indication of powder flow

(*May be improved by glidant, e.g. 0.2% Aerosil)

Flow	Angle of repose	Carr's index (%)
Excellent	<20	5-15
Good	20-30	12-16
Fair to passable*	30-34	18-21
Poor	> 40	23-35
Very Poor		33-38
Extremely Poor		>40

Melting Point

The melting point, or freezing point, of a pure crystalline solid is defined as the temperature at which the pure liquid and solid exist in equilibrium. The melting point of a substance is the temperature range over which the first crystal of a solid just starts to melt and the last crystal completes its melting. Drugs with a low melting point may soften during a processing step in which heat is generated, such as particle size reduction, compression, etc. Also, the melting point or range of a drug can be used as an indicator of purity of chemical substances. The presence of even a small amount of impurity will lower a compound's melting point by a few degrees and broaden the melting point temperature range.

Rule-of-thumb- 1 % of foreign substance will result in a 0.5 °C depression.

Techniques of melting point determination

The melting of a drug can be measured using these techniques:

- Capillary melting
- Hot stage microscopy
- Differential scanning calorimetry or thermal analysis.

Differential scanning calorimetry and differential thermal analysis (DSC & DTA)

DTA measures the temperature difference between the sample and a reference as a function of temperature or time when heating at a constant rate. DSC is similar to DTA, except that the instrument measures the amount of energy required to keep the sample at the same temperature as the reference, i.e. it measures the enthalpy of transition.

Polymorphism

Drug substances can exist in more than one crystalline form with different lattice arrangements. This property is termed polymorphism. The different polymorphs vary in physical properties such as solubility, dissolution, solid state stability as well as processing behavior in terms of powder flow and compaction during tableting.

For example the metastable forms of chloramphenicol palmitate and chlortetracycline hydrochloride exhibit improved rate and extent of bioavailability.

Polymorphic transitions can also occur during milling, granulating, drying and compressing operations (e.g. transition during milling for digoxin). Various techniques are used to determine

crystal properties. The most widely used methods are hot stage microscopy, thermal analysis, infrared spectroscopy, and x-ray diffraction.

Solubility

A drug must possess some aqueous solubility for therapeutic efficacy. For a drug to enter the systemic circulation and exert a therapeutic effect, it must first be in solution. If the solubility of the drug substance is less, consideration must be given to improve its solubility. Chemical modification of the drug into salt or ester forms is frequently used to increase solubility.

Table: Descriptive solubilities

Descriptive term	**Parts of Solvent required for Part of Solute**
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or Insoluble	10,000 or more

Intrinsic solubility (C_o)

The solubility values obtained in acid for a weak acid or alkali for weak base can be assumed to be the intrinsic solubility (C_o), i.e. the fundamental solubility of the drug when completely unionized.

However accurate solubility is determined by the use of a phase-solubility diagram. The data are obtained from a series of experiments in which the ratio of the amount of drug to the amount of dissolving solvent is varied. Any deviation from the horizontal is indicative of impurities, which a higher drug loading and its inherent impurities either promotes or suppresses solubility.

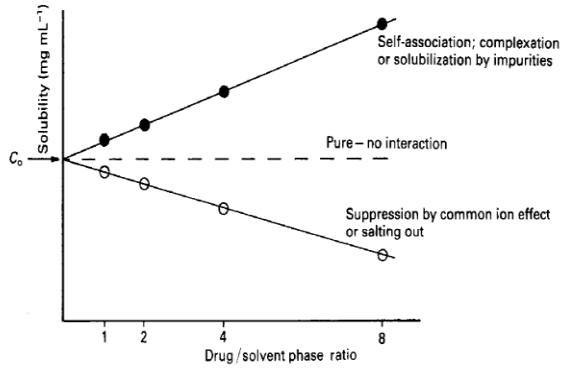

Fig: Effect of drug: solvent ratio on solubility when the drug is impure

pKa/ Dissociation Constant

pKa may be defined as the pH at which a drug is 50% ionized. Cell membranes are more permeable to the unionized forms of drugs than to their ionized forms, mainly because of the greater lipid solubility of the unionized forms and the highly charged nature of the cell membrane, which results in binding or repelling of the ionized drug and thereby decreases cell capability.

The concept of pKa is derived from the Henderson-Hassel Balch equation.

For an acid:

$pH = pK_a + \log$ [Ionized concentration (Salt)/ Un-ionized concentration (acid)]

Since the pH of body fluids varies (stomach, pH 1; lumen of the intestine, pH 6.6; blood plasma pH 7.4), the absorption of a drug from various body fluids will differ and may dictate to some extent the type of dosage from and the route of administration preferred for a given drug.

Rearranging the equation for an acid yields

pK_a – pH = log[Un-ionized concentration (acid)/ Ionized concentration (salt)]

By that equation we can determine the relative extent to which a drug remains unionized under various conditions of pH. For example, if a weak acid having a pK_a of 4 is assumed to be in an environment of gastric juice with a pH of 1, the left side of the equation yields the number 3, which means that the ratio of un-ionized to ionized drug particles is about 1000:1 and gastric absorption will be excellent.

Dissolution

Dissolution rate is the time it takes for the drug to dissolve in the fluids at the absorption site. Dissolution rate can affect the onset, intensity, and duration of response and control the overall bioavailability of the drug from the dosage form.

The dissolution of a drug is described by the general Noyes-Whitney equation-

$dm/dt = KA (Cs - C)$

Where dm/dt is the dissolution rate, K is the dissolution rate constant, A is the surface area of dissolving solid, Cs is the concentration of drug in the saturated diffusing layer and C is the concentration of drug in the dissolution medium at time t.

During the early phase of dissolution, $Cs \geq C$ and if the surface area (A) and experimental condition are kept constant then k can be determined for compacts containing drug alone. The constant K is now termed the intrinsic dissolution rate (IDR) constant and is a characteristic of each solid drug compound in a given solvent under fixed experimental condition. Drugs with values of K below $0.1 mg^{-1} cm^{-2}$ usually exhibit dissolution rate-limiting absorption.

Intrinsic dissolution rate-

It is the dissolution rate of pure drug at constant surface in a given solvent under fixed experimental condition. IDR is independent of formulation effects and measures the intrinsic properties of the drug.

Measurement of intrinsic dissolution rate

A compressed disc of material can be made by slow compression of 500mg of drug in a 13mm IR disc punch and die set to a high compaction pressure greater than 500 MPa (to ensure zero porosity) and long dwell time (to improve compaction). The metal surfaces in contact should be pre lubricated with, for example, stearic acid (5%w/v in chloroform). The compressed disc is fixed to the holder of the rotating basket apparatus using a low melting paraffin wax and successively dipped so that the top and sides of the disc are coated. The lower circular face should be cleared of residual wax using a scalpel and carefully scraped remove any stearic acid transferred from the punch face.

The coated disc is rotated at 100 rpm, 20 mm from the bottom of a 1 litter flat-bottomed dissolution flask containing 1 liter of fluid at 37^0C. The amount of drug release is then monitored, usually by UV spectrometry, with time.

Log P/k_w^o (Partition coefficient)

Partition coefficient is a measure of the relative solubility of a drug in other solvents compared with its solubility in water. As an example, if the drug it twice more soluble in an oil than water, it will have a k_w^o of 2.

When these ratios are much larger, it is common practice to use the logarithmic ratio, log P (i.e. the log of partition coefficient, log P = log [k_w^o]). For example, a [k_w^o] of 1000 is the same as a log P of 3. Thus higher a drug's [k_w^o] or log P, the greater its oil solubility compared with its aqueous solubility.

Determination of partition coefficient-

Shake Flask Method is used to determine partition coefficient of the drugs. In this method the drug, predissolved in one of the phases, is shaken with the other partitioning solvent for 30 minutes, allowed to stand for 5 minutes and lower aqueous phase (octane has a density of 0.8258 g mL^{-1} and therefore rises to the top) is assayed.

Hyperdiscriminating solvents- Solvents that are less polar than octanol are termed hyperdiscriminating e.g. heptane, toluene, benzene, cyclohexane etc.

Hypodiscriminating solvents- If the transfer of the solute to the oil phase is small and to encourage greater movement of drug from aqueous layer, a considerable more polar non-aqueous solvent are used. Solvents that are more polar than octanol are termed as hypodiscriminating e.g. butanol and pentanols etc.

Wetting

Wetting agents are surfactants like tweens, spans, poloxamers etc., which reduce the interfacial tension between the particles and the liquid vehicle and promotes wetting and solubilization.

Wetting agents are used in liquid dosage forms to create a homogenous dispersion of solid particles in a liquid vehicle. Wetting agents are Surfactants (HLB Value 7 to 9) that when dissolved in water, lower the contact angle and aid in spreadability of water on the particles surface to displace the air layer at the surface and help in wetting and solubilization.

Dielectric constant

Dielectric constant of compounds also gives an indication of their polarity and hence extent of solubility. The dielectric constant of non polar compounds range between 1 to 20 and polar compounds have dielectric constant of more than 50. Compounds with dielectric constant between 26 and 50 are described as semi- polar.

Very polar (hydrophilic) solute such as urea is very soluble in highly polar water, less soluble in fairly polar methanol, and practically insoluble in non-polar solvents such as benzene. Similarly a non-polar or lipophilic solute such as naphthalene is insoluble in water, fairly soluble in methanol, and highly soluble in non-polar benzene.

Hygroscopicity

Many drugs lose or gain some water from the surrounding atmosphere, depending on the relative humidity (RH). A substance which absorbs sufficient moisture from the atmosphere to dissolve itself is deliquescent. A substance which loses water to a lower hydrate or becomes anhydrous is termed efflorescent. Materials unaffected by RH are termed non- hygroscopic while those in a dynamic equilibrium with water in the atmosphere are hygroscopic.

Pharmaceutical air conditioning is usually set below 50% RH and very hygroscopic products, e.g. effervescent tablets that are particularly moisture sensitive, are made and stored below 40% RH.

Hygroscopicity Classification

Classification	Criteria- % water uptake at 25°C/80% RH in 24 h
Class- I, Non-hygroscopic	-
Class- II, Slightly hygroscopic	Increase in mass, $< 2\%$ & $\geq 0.2\%$
Class- III, Moderately hygroscopic	Increase in mass, $< 15\%$ & $\geq 2\%$
Class- IV, Very hygroscopic	Increase in mass $\geq 15\%$