UNIT I

Preformulation

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INTRODUCTION

Preformulation testing is the first step in the rational development of dosage forms.

It can be defined as “an investigation of physical and chemical property of a drug substance alone and when combined with excipients.”

Physiochemical properties are those that can be determined from *in vitro* experiments.
The main objective is to generate information useful to the formulation in developing most stable and bioavailable dosage form that mass can be produced.
Why is Preformulation Important

- It describes the process of optimizing the delivery of drug thorough determination of physical, chemical properties of new drug molecule that affect drug performance and development of an efficacious stable and safe dosage form.

- Preformulation studies on a new drug molecule provide useful information for subsequent formulation of a physicochemically stable and biopharmaceutically suitable dosage form.
Once pharmacologically active compound has been identified different project team have responsibility for assuring that compound enters in development process in it`s optimum molecular form.

If deficiency is detected then project team decide on molecular modification. e.g. salts, prodrug, solvets, polymorphs,

Mostly salt & prodrug approaches are common.

Most salts of organic compound are formed by addition or removal of proton to form ionized drug molecule which is then neutralized with counter ion.

E.g. ephedrine hydrochloride.
Organic salts are more water soluble than un-ionized molecule.

Prodrug are synthetic derivative of drug molecule

Pharmaceutical improvement from prodrug include stabilization, increase or decrease of solubility, crystallinity, taste, odour.

e.g. Erythromycin esolate

Once the optimum molecular form of drug has been selected formulation development begin there task in drug development process.
BULK CHARACTERIZATION

- CRYSTALLINITY & POLYMORPHISM
- HYGROSCOPICITY
- FINE PARTICLE CHARACTERIZATION
- BULK DENSITY
- POWDER FLOW PROPERTIES

STABILITY ANALYSIS

- STABILITY IN TOXICOLOGY FORMULATION
- SOLUTION STABILITY
- PH RATE PROFILE
- SOLID STATE STABILITY
- BULK STABILITY
- COMPATIBILITY

SOLUBILITY ANALYSIS

- IONIZATION CONSTANT – Pka
- PH SOLUBILITY PROFILE
- COMMON ION EFFECT – Ksp
- THERMAL EFFECTS
- SOLUBILIZATION
- PARTITION COEFFICIENT
- DISSOLUTION
1. Bulk properties of the solid form such as crystallinity, polymorphism, particle size, powder flow property, and surface characteristics are likely to change during process development.

A. Crystallinity

- The crystal habit describes the outer appearance of crystals (platy, equant, needle, bladed, etc.) and internal structure is arrangement within solid.

- Compounds have several different habits, depending on the environment for growing crystals.
Changes with internal structure alter crystal habit while chemical changes produces both change in internal structure & crystal habit.

- Characterization of solid form involves –
- Verifying that the solid is expected chemical compound.
- Characterizing internal structure
- Describing habit of crystal.

The internal structure of compound can be classified in following way.
Chemical compound

- Internal structure
  - crystalline
  - amorphous

- Molecular adduct
  - Nonstoichiometric inclusion compound
  - Stoichiometric solvates (hydrates)

- Single entity
  - Single
  - Polymorphs

- Channel
  - Layer
  - Cage (clathrate)
A crystalline compound may contain either a stoichiometric or nonstoichiometric amount of crystallization solvent.

Nonstoichiometric aducts are called as inclusions or clathrates.

Stoichiometric aducts are called as solvets molecules.

E.g. Chloramphenicol palmitate A, B, C & amorphous form are used in suspension then after investigation it was found that form B have increased peak serum level due to more soluble form.
Analytical method used for characterization

- Microscopy
- Differential scanning calorimetry
- Infrared spectroscopy
- Thermogravimetric analysis
- X-ray diffraction
**MICROSCOPY:**

- In this technique substances are examined under the microscope.

- It gives information about shape, thickness, particle size, etc. of drug molecules.

- By this method we can study crystal morphology, difference between polymorphic character of molecule.
In DSC, the sample & the reference material are subjected to linear heating, but the temperature of two materials should be the same, and a graph is plotted.

E.g. Doxorubicin.

In both Differential Scanning Colorimetry & Differential Thermal Analysis the heat loss and gain resulting from physical or chemical transitions occurring in a sample.

Enthalpic changes both endothermic & exothermic are caused by phase transitions.

For example, fusion, sublimation, solid-solid transition & water loss generally produce endothermic effects while crystallization produces exothermic effects.
Differential Scanning Colorimetry

\[ \Delta H_f = 10.45 \text{ kcal/M} \]
\[ \text{S.D.} = 2.9 \ (28\%) \]
Infrared spectroscopy

- The study of the interaction of electromagnetic radiation with vibrational and rotational resonances within a molecular structure is termed as IR Spectroscopy.

- IR has the ability to differentiate isomers groups such as Cis-trans double bond compound.

- Gives an information regarding functional group present in new drug molecule.

- FT-IR use for both qualitative and quantititative analysis of sample.
Thermal Gravimetric Analysis

- It is an **excellent analytical procedure** for determination of the content of moisture.

- TGA helps to **determine the temperature** at which the material losses weight due to evaporation or decomposition.

- E.g. Cefamandole Naftate.

- Weight loss begins at 63°C & loss continues at 137°C & at 163°C resulting decomposition.

- Determine the temperature at which no loss of weight takes place; this indicates the stability of the compound.
X-RAY DIFFRACTION

- When a beam of non-homogenous x-rays is allowed to pass through a sample, the x-ray beam is diffracted and it is recorded by means of photographic plates.

- Single Crystal X-ray provides the most complete information about the solid state.

- It is used to differentiate the amorphous and crystalline forms.

- This method is tedious, time consuming, and hence unsuitable for routine use.
B. Polymorphism

- Polymorphism is the ability of the compound to crystallize as more than one distinct crystalline species with different internal structure.

- Formation of different polymorphs depends on solvents, temperature, pressure, rate of cooling, etc.

- Polymorphic transitions can also occur during milling, granulating, drying and compressing operations.

- Different polymorphs vary in physical properties such as dissolution, solid-state stability, compatibility, etc.
C.HYGROSCOCITY

- The tendency of a solid to take up water from the atmosphere, as it is subjected to a controlled RH program under isothermal condition i.e. hygroscopicity.
- Deliquescent materials adsorbs sufficient water to dissolve completely.
- Changes in moisture level can greatly influence many parameters e.g. chemical stability, flowability, compactibility.
Analytical method used for characterization.

- Sample of bulk drug are placed in open containers with a thin powder bed to assure maximum atmospheric exposure. These samples are then exposed to range of controlled relative humidity environment prepared with saturated aqueous salts solution.

- Other method used are TGA, Karl fischer titration & gas chromatography.
D. fine particle characterization

- Study of particle size give an information about solubility, dissolution rate, absorption, etc.

- Particle size and surface area of a solid drug are inversely related to each other.
  - Eg: Griseofulvin
Analytical method used for characterization.

- Light microscope with calibrated grid
- Stream counting devices e.g. coulter counter, HIAC counter
- Sieve analysis & Image analysis
- BET nitrogen adsorption
- Scanning electron microscopy
E. Powder flow property

- The flow properties of a powder will determine the nature and quantity of excipients needed to prepare a compressed or a powder dosage form.

- This refers mainly to factors such as the ability to process the powder through machines.

- Powder are classified as free flowing & non free flowing

- This subject comes paramount when attempting to develop a solid dosage form containing large percentage of cohesive material.
Analytical method used for characterization.

- Free flowing powders may be characterized by simple flow rate apparatus consisting of grounded metal tube from which drug flows through an orifice onto an electronic balance which is connected to strip chart recorder.
- Another method used is compressibility.

- Cohesive powders are characterized by tensile testing or evaluated in shear cell.
2. SOLUBILITY ANALYSIS

A. Drug pKa / Ionization constant

- pKa is the dissociation constant of a drug.

- The unionized substances is lipid soluble thus dissolve in lipid material of the membrane and transported by passive diffusion.

- Where as, the ionized substances is a lipid insoluble therefore permeation is slow.
The percentage of ionization can be calculated as ...

For Acidic compounds:

\[ \text{PH} = \text{pKa} + \log \frac{\text{ionized drug}}{\text{un-ionized drug}} \]

For Basic compounds:

\[ \text{PH} = \text{pKa} + \log \frac{\text{un-ionized drug}}{\text{ionized drug}} \]

Degree of ionization depends up on the pH. for acidic drugs pKa ranges from 3-7.5. for basic drugs pKa ranges from 7-11.
Analytical method used are

- UV and Visible Spectrophotometry
- Potentiometric titrations
UV and Visible Spectrophotometry

- When organic molecules in solution, or as liquid, are exposed to light in the visible and ultraviolet light regions of spectrum, they absorb light of particular wavelengths depending on the type of electronic transition that is associated with the absorption.

- The electronic transitions depend on the electron bonding within the molecule.

- Spectrophotometry can be used to study enzyme reactions and to evaluate the effect of drug on enzyme.

- UV study of compounds gives information regarding unsaturation of compounds.
Compounds with acidic/basic functionalities show pH dependent solubility profile.

\[ \text{pH} = \text{pKa} + \log \frac{[Cs]}{[Ca]} \]

- \( \text{pKa} \) — negative log of the ionization const.
- \([Cs]\) — molar conc. of salt form in water
- \([Ca]\) — molar conc. of free acid in water.

Total solubility can be given as

\[ S_t = [Ca] + [Cs] \]
Solubility Analysis

1. **Aqueous Solubility:** it is the sum of the individual solubilities for the neutral compound and all ionized species present. For compounds with ionizable groups, aqueous solubility is a function of pH.

2. **Intrinsic solubility:** It is defined as the number of moles per liter of solute that dissolves into solution. Equilibrium between solute and solution is maintained at a specific temperature, usually 25°C. Units can be expressed as mol/l, mg/ml.
### C. PARTITION COEFFICIENT

- **Partition coefficient influence permeation of a drug across biological membrane.**

- **Partition coefficient is a ratio of equilibrium concentration of drug in oil phase to equilibrium concentration of drug in aqueous phase.**

\[ K = \frac{C_o}{C_w} \]

where,  
- \( C_o \) - organic phase concentration  
- \( C_w \) - aqueous phase concentration
D. DISSOLUTION

- To know the gastrointestinal absorption & other physicochemical properties.

- The intrinsic dissolution rate is determined by the rotating disc method.

- The dissolution rate is described by Noyes-Whiteny equation.

- Analytical method used are
  - Chromatography
  - UV and Visible Spectrophotometry
In the preformulation studies, chromatographic techniques such as TLC, HPLC, GC carrying a major role.

The major advantages are direct analysis of aqueous samples, high sensitivity, and specific determination of drug concentration, separation of drug from impurities or degradation products.

Analytical data from TLC may be required to precisely determine the kinetics of decomposition.

HPLC and GC are useful for solubility measurements.
In this study includes both solutions and solid-state experiments under various conditions for handling, formulation, storage, and in vivo administration.

- Solution phase stability: The effect of pH on stability is important in the development of both oral and Parenteral dosage forms.

- Acid sensitive drugs protected from highly acidic environment of the stomach by coating it with suitable polymers.

- Solid phase stability depends on several factors like temperature, pH, humidity, hydrolysis, oxidation, etc...
The purpose of stability testing is to assess the effect of temperature, humidity, light, and environmental factors on the quality of the product. Above data is used for predicting the shelf life. Potency should not lose under the recommended storage condition. Prediction of storage conditions is also important.
DRUG DEGRADATION MECHANISM

- Hydrolysis
- Solvolysis
- Oxidation
- Photolysis
- Metal chelating
STABILITY TYPE

TWO TYPE:-

- 1. Solid state stability
  - Tablet & capsule
  - Free moisture (2% req. for compression)
- 2. Liquid state stability
  - Selection of granulation solvent
  - Study when exposed to G.I. fluid (erythromycin)
Factor affecting solid dosage form stability

- Moisture
- Excipient:
  - starch & povidone more water content
- Suppository base cause degradation of aspirin
- Temperature (polymorphism)
- Light & oxygen
Factor affecting liquid dosage form stability

- $p^H$:
- Catalytic effect of $H^+$ & $OH^-$ ions.
- Hydrolysis in solution
- Temperature: - Arrhenius equ.
- Solvent effect:
CONCLUSION

- Preformulation studies on a new drug molecule provide useful information for subsequent formulation of a Physicochemically stable and Biopharmaceutically suitable dosage form.

- Thorough Preformulation work is the foundation of developing efficacious and economical formulations.
REFERENCES


