PREFORMULATION STUDY

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The Theory
ıd Practice of Industrial
Pharmacy

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THIRD EDITION
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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.

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

OBJECTIVES

- The main objective is to generate information useful to the formulation in developing most stable and bioavailable dosage form that mass can be produced.

PHYSICOCHEMICAL PROPERTIES

1. BULK PROPERTIES

- 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.

Crystallinity

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

- Compounds have several different habits, depending on the environment for growing crystals.

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

Particle size

- 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

Powder flow property

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

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

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.

- Classified based on the amount of rate of water uptake when a solid is exposed to controlled RH value at a specified temperature.

1. AQUEOUS SOLUBILITY

- Important goal of the preformulation effort is to devise a method for making solutions of the drug
- Orally administered drug must dissolve in the aqueous fluid of the GIT prior to absorption.
- Solubility can be improved by addition of cosolvents.
- Solubilities cannot be determined by precipitative methods.

2. Drug pKa / Ionization at physiological pH

- pKa is the dissociation constant of a drug.
- The nonionized 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:

$$\% \text{ ionized} = 100/\ 1 + \text{antilog}\ (pKa - pH)$$

For Basic compounds:

$$\% \text{ ionized} = 100/\ 1 + \text{antilog}\ (pH - pKa)$$

- 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.

3. 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 .

$$K=C_o/C_w$$

where, C_o-organic phase concentration

C_w-aqueous phase concentration

- Following administration, the drug must travel through a variety of membranes to gain access to the target area.

- Drug with extremely high partition co-efficient (i.e. very oil-soluble) readily penetrate the membranes.

- While drugs with excessive aqueous solubility i.e. low oil/water partition co-efficient cannot penetrate the membrane.

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

✓ Intrinsic dissolution
✓ Paricular dissolution

STABILITY ANALYSIS

DRUG STABILITY

- 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...

COMPATIBILITY

- Compatibility test play a very important role in the preformulation studies of oral dosage forms.

- Problems arise because of the *interaction* with other drug substances and with preservatives, stabilizers, dyes, and flavors.

- It is important for the formulator of a new drug substance to know with which excipients he can work and which he cannot.

ANALYTICAL MEASURES

Various analytical techniques are available for the investigation of the physicochemical properties and determination of impurity of new drug molecules.

These includes:

1. Microscopy
2. Spectroscopy
3. Chromatography

A. 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.

B. SPECTROSCOPY

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 depends on the electron bonding with in the molecule.

- Spectrophotometry can be used to study to enzyme reaction and to evalute the effect of drug on enzyme.

- UV study of compounds gives information regarding unsaturation of compounds.

IR 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 quqntitative analysis of sample.

X-RAY DIFFRACTION

- When a beam of non homogenous x-rays is allowed to pass through a sample the x-ray beam is diffracted & 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 amophous and crystalline forms.

- This method is tedious, time consuming & hence unsuitable for routine use.

Thermal Analysis

- Differential scanning calorimetry (DSC) and differential thermal analysis(DTA) are particularly useful in preformulation studies including purity, polymorphism, solvation, degradation, and excipient compatibility.

- It measures physical or chemical changes of drug molecules.

Thermigravimetric analysis

- Used to detect the existange and stability of solvated drug molecule.

C. CHROMATOGRAPHY

- 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.

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.

THANK YOU