# *MODULE 1: Preformulation Studies*

## *Lecture 1*

DISCLAIMER

All the content material provided here is only for teaching purpose

# Introduction

## Preformulation:

- A Formulation development stage during which the physicochemical properties of drug substance are characterized.
- Quantitation of physical and chemical properties that will assist in developing a stable, safe and effective formulation with maximum bioavailability

# The Drug Development Cycle

The process of developing a new drug can take between 10 and 15 years with an estimated average cost of $800 million

# Requirement of preformulation studies

- Preformulation studies are an important foundation tool early in the development of both API and drug products.

Influences

- ✓ Selection of the drug candidate itself

  Selection of formulation components
- ✓ API & drug product manufacturing processes
- ✓ Determination of the most appropriate container / closure system
- ✓ Development of analytical methods

  Toxicological strategic management process

# PreformulationCharacterization

- Organoleptic
- crystallinity and polymorphism water adsorption
- particle size, shape, and surface area
- bulk density

  Adhesion
- powder flow

  compressibility
- Bulk properties
- solubility

  analysis

  Ionization
- partition

  coefficients

  dissolution

**Stability**

- solid state (RH, oxygen, light, compatibility)
- solution (pH, buffers, solvent, temperature)
- compatibility with ex

# Solubility Analysis

- Ionization constant
- pH solubility profile
- Common ion effect
- Thermal effect
- Solubiization
- Partition coefficient
- Dissolution

# Organoleptic Characterization

- **COLOR**

1. Off white
2. Green yellow
3. Tan
4. Shiny

- **ODOUR**

1. Pungent
2. Sulhrous
3. Fruity
4. Aromatic
5. Odourless

- **Taste**

1. Acidic
2. Bitter
3. Intense
4. Sweet
5. Tasteless

# Principal areas of Pre-formulations

Bulk Characterization

Solubility Analysis

Stability Analysis

# Principal

## Bulk Characterization

Crystallinity and polymorphism

Hygroscopicity

Fine particle characterization

Bulk density

Powder flow properties

# Bulk Characterization

- A drug candidate – Solid form not identified – emerge of new polymorphs
- Solid form – particle size, bulk density and surface morphology – Process development
- Comprehensive characterization – To avoid misleading predictions of stability or solubility, which depends on a particular crystalline form

# Crystallinity

- Crystal habit and the internal structure affects the bulk and physiochemical properties
  - **Crystal Habit** – Description of the outer appearance of a crystal. Eg: Acicular or needle, platy, massive, tabular etc
  - **Internal structure** : Molecular arrangement within the solid

# Crystallinity and polymorphism

Changes in internal structure for a compound – Alter change in the crystal habit.

Characterisation Involves –

- Verifying the solid is the expected chemical compound
- Characterization the internal structure
- Describing the habit of the crystal



Prismatic

Bladed

- Crystals are characterized by Repetitious spacing of constituent atoms or molecules in 3 dimensional array
- Amorphous Form-

Atoms or molecules are randomly placed, prepared by Rapid precipitation

Lyophilization

Rapid cooling of liquid melts

- Amorphous – Higher thermodynamic energy, solubilites and dissolutions is also high.
  - ✓ Upon storage – Tends to revert more stable forms
  - ✓ Disadvantages: Thermodynamic instability

# Crystallinity and polymorphism

- Crystalline–
- Nonstoichiometric adducts – entrapped solvents within crystals.
- Undesirable, Lack of reproducibility – Avoided
- Stoichiometric adducts – As a solvate, is a molecular complex that has incorporated the crystalline solvent molecules into specific sites within crystal lattice
- Eg.: water ( hydrate- monohydrate)

# References

1. Lachman L Lieberman H.A, Kanig J.L, The Theory and Practice of Industrial Pharmacy, 3rd edition.