Chapter 1

Preformulation I
(Physical Form: Crystal & Amorphous)

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API/ Drug

"API or drug is a chemical entity with affinity to the receptors and with positive or negative or nil intrinsic activity."

- **Timing of Preformulation**

  After Preclinical trial

Before formulation development

- Or in case of developing a new dosage form of an existing API.
- API is never administered in a raw chemical form.
- Excipients + Drug (API) + Dosage form.
- Focus of Preformulation
- High degree of uniformity: in physical characteristics (weight. Content, hardness etc) and drug release.
- Physiological availability, Bioavailability
- Therapeutic quality.

Preformulation

"All the activities of characterization of physicochemical properties of the drug under study which are important to develop a stable effective and safe dosage form."

Challenges in Preformulation

- Very small amount of API available.

- In initial stage of drug discovery, we have only a very tiny amount of API available sometimes in few mg, that too impure.
- Only preliminary data like melting point, spectral data and structure is available.

Preformulation Properties

- ***Physical properties:*** Physical form (crystal & amorphous), polymorphism, particle size, shape, flow properties, solubility profile (pKa, pH, partition coefficient),
- ***Chemical Properties:*** Hydrolysis, oxidation, reduction, racemisation, polymerization
- BCS: dissolution & permeability

Planning Preformulation

- First identify the dosage form
- Pick and study the relevant physicochemical properties (as per the desired dosage form) and take it in priority.
- Consequences of poor PF
- A poor Preformulation study may lead to the disasters
- Unstable/ ineffective or less effective and unsafe dosage form
- Loss of development time
- Increased expenditure on development
- Triggering repeated need for in vivo bioavailability/bioequivalence studies
- Physical properties

Solid state is the most preferred state of API for developing any dosage form. **Why?**

- API can easily be crystallized
- Easily be purified (by crystalizing)
- Easy to handle than liquids
- Better chemical stability than that of liquids.
- Types of solids

Solids may be of three types as per the internal structure (Physical)

- Amorphous
- Liquid Crystal
- Crystal

Amorphous Form

- ***"These are the solids which do not exhibit long-range order in any of the three physical dimensions."***
- There may be short-range order for amorphous solids.
- The amorphous phase always show higher free energy, enthalpy, and entropy than the crystalline one.

Amorphous form	→	Small particle size	→
More hygroscopic	→	More surface area	→
More energy (more reactivity)	→	Less stability	

Use of Amorphous Form

- In improving solubility
- In improving the oral bioavailability of the poor water soluble drugs.

But these are **less stable** as compared to their crystal phase.

There exists **some amount of crystal form in amorphous forms** also **(Two state model : USP).**

- The challenge
- Stability issues
- They might change in to crystalline form with the passage of time
- Very hygroscopic
- Prone to hydrolytic degradation.
- Typical to be formulated
- Only few amorphous drugs containing dosage form are marketed and approved by FDA.

Some FDA approved amorphous drugs

- **Itraconazole,**
- **Nelfinavir mesylate**
- **Paroxetine**
- **Celecoxib**
- **Cefuroxime axetil**
- **Cefepodoximeproxetil**
- **Novobiocin**

So, the amorphous form should be avoided until the difference in solubility make a significant impact on bioavailability.

Liquid Crystals

"If the internal structure is having long-range order but only one or two dimensions"

- On the basis of number of components these can be further classified as single, binary, and ternary LCs.
- But these are not of much use in pharmaceuticals.

Crystal Form

- A majority of APIs are crystalline in nature.
- **"the solids with the internal structure having long-range order in all three dimensions."**
- The logical method of classification of crystal is based on **the angle between the faces.**
- If three dimensions are given by a, b, and c, then these crystals may be of several types on the basis of length of the faces and angle between these faces.
- If a=b=c and angle between all the faces is 90 degree it is called simple cubic crystal (three equal axes each at right angle)
- Different crystal forms

Crystal Habit

Moving to It is the relative development of different types of faces. Let's take the example of

- NaCl in aqueous solution → Crystallizes into → Cubic face
- NaCl in aqueous solution → Crystallizes in to → Octahedral faces (with small amount of Urea)

The crystal habit depend on the process, impurities or conditions. (It refers to the types of faces developed and not the shape of the faces)

Single Entity

"The ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in a crystalline lattice is called polymorphism."

- If the drug forms a binary composite of crystalline lattice with another chemical it is called binary adduct. And so on like ternary …
- On the basis of the ionization states of these species the adducts may be ionic, molecular or ionic/molecular.

Cocrystals

- "Two or more molecules are hydrogen bonded to each other."
- The choice of **cocrystal formation, depends on the need**.
- **Caffeine-oxalic acid cocrystals** showed better stability even at high humidity (Tarsk et al. 2005).
- **Carbamazepine-sachharin cocrystals** showed better bioavailability, suspension stability and same stability as compared to its immediate release tablet (Hickey 2007).

Importance of Crystallinity

- Solubility of drug candidates can be altered by modifying the crystal form:
- Solubility can be improved by partial amorphization through developing adducts or binary composites of drug.
- **Onset of action** can be controlled by using the crystalline form.
- Crystalline form can delay the onset of action and prolong the drug release. If you mix both of the form you can modulate the release. **For example: lente insulin give quick action and prolonged release.**
- The purity standards are laid down by the properties of a pure crystal.

FDA States

"It is mandatory to establish whether or not the API being studied exist in more than one crystalline form. If yes, what are the properties of all different crystal forms. Like melting point, solubility, stability, safety and efficacy."

How Crystals Affect Solubility

- When a crystalline molecule is to be dissolved, firstly it is to come out from the crystal lattice. The amorphous solute molecule are free to move in a solvent so easily dissolved.
- THE ENTHALPY CONSIDERATION delays the entry of drug molecule from crystalline lattice to solvent.

Characterization

- **Melting point**
- **Capillary melting**
- **Hot stage microscopy**
- **Thermal analysis or Differential Scanning Calorimetry (DSC)**
- **X ray diffraction**
- **IR**
- **SEM**
- **Misc.: Synchrotron radiation, solid state raman spectroscopy, solid state NMR etc.**

Thermal Analysis

- **The most versatile and precise method.**
- **Most suited for preformulation (requires only 2-5 mg of sample).**
- In Differential Thermal analysis **(DTA)** sample is heated at a constant rate and difference of the temperature between the sample and a reference is measured as a function of temperature or time.
- In DSC, all things are same like DTA except additional measurement of enthalpy or energy required to keep the sample at same temperature as that of reference.

X Ray Powder Diffraction

X rays are EMR between UV and gamma rays. These are expressed in angstrom units.

When X rays are incident on crystalline solids, scattering of x rays takes place. This scattering is called diffraction.

This diffraction is unique for a single pure crystal.

And it is available in the repositories XRD data bank.

Bragg's law define the diffraction

$$n\lambda = 2d \sin \theta$$

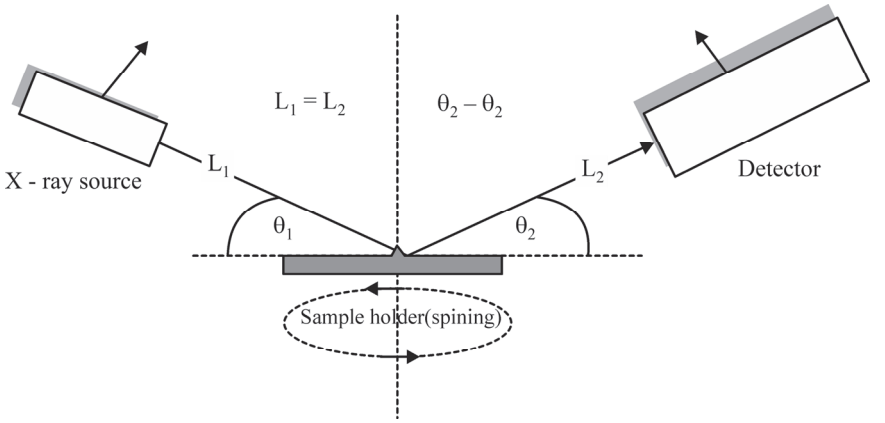
Where λ is wavelength of a perfectly and monchromatic X-ray beam

θ is the angle of incident beam on crystalline sample

n is the order of reflection (an integer, usually 1)

d is the distance between planes in crystal

Concept of XRD



Infra Red Spectroscopy

- Provides qualitative information
- Different arrangement of atoms different molecular environment different stretching frequencies.
- Used to distinguish a polymorphic form.
- Functional groups, change, and interactions may be detected.
- Official books possess a data bank of IR of standard drugs.
- Aids to XRD in confirming the purity of molecule.
- Scanning Electron microscopy (SEM)
- The most advanced technique of visualizing the surface and also for particle size measurement.

Miscellaneous Method

- Synchrotron radiation,
- Solid State Raman Spectroscopy,
- Solid state NMR etc.

Take away Message

- Preformulation is the heart of formulation development
- Safety, stability and efficacy
- Amorphous form- unordered form, more soluble, high free energy, less stable
- Crystal form- defined shape, less soluble, more stable, less free energy
- Can be characterized by XRPD, IR, DSC and SEM