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IFTM University, Moradabad, Uttar Pradesh
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E-Content

IFTM University, Moradabad

PRE-FORMULATION

Part 1

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Content

- Introduction to the Industrial Pharmacy.
- Introduction to Preformulation.
- Goals and objectives (Major area of preformulation research)
- Study of Physico – Chemical Characteristics of Drug Substances

INTRODUCTION

- ❖ Prior to development of a formulation or dosage form, it is essential that certain properties of a drug molecule are to be determined.
- ❖ This information decides many of the subsequent events and approaches in formulation development.
- ❖ **Preformulation** is the phase of research and development in which the physical and chemical properties of a drug molecule is studied in order to develop safe, effective and stable dosage form.
- ❖ **Preformulation** commences when a newly synthesized drug shows a sufficient pharmacological promise in animal model to warrant evaluation in man.
- ❖ It is the First step in rational development of a dosage form of a drug substance.

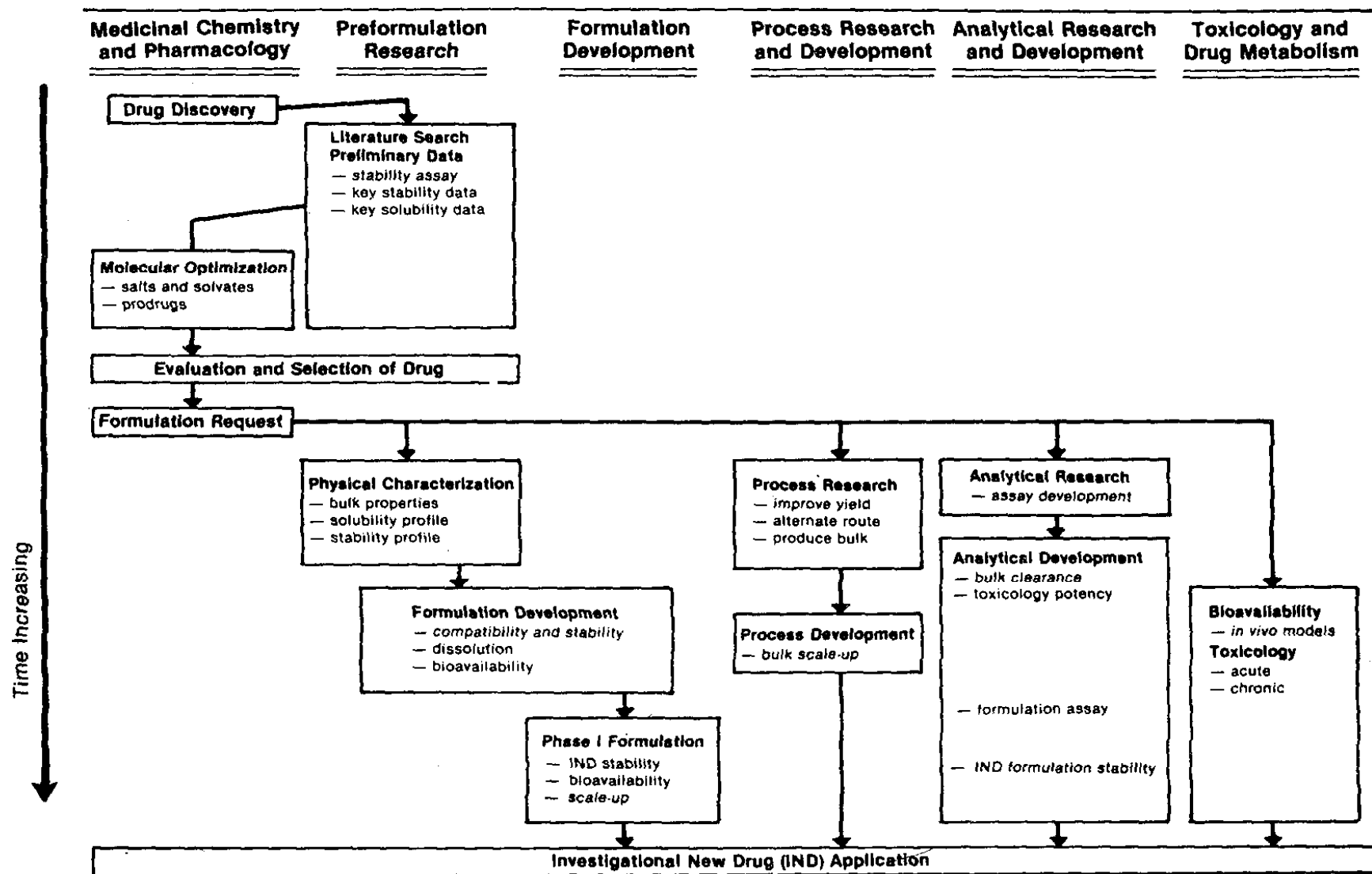
GOALS & OBJECTIVES

- ❖ To generate information useful to the formulation in developing **most stable and bioavailable dosage form** that can be produced.
- ❖ **To Establish necessary physico - chemical parameters of new drug** substance that can affect the drug performance and development of an efficacious stable and safe dosage form.
- ❖ Establish physical characteristics.
- ❖ Establish compatibility with common excipients.
- ❖ Provide insights into how drug products should be processed and stored to ensure their quality.
- ❖ To develop an optimal drug delivery system.

- I. Compound Identity:**
- II. Structure:**
- III. Formula and Molecular Weight:**
- IV. Therapeutic Indication:**
 - Probable Human Dose:
 - Desired Dosage Form(s):
 - Bioavailability Model(s):
 - Competitive Products:
- V. Potential Hazards:**
- VI. Initial Bulk Lots:**
 - Lot Number:
 - Crystallization Solvent(s):
 - Particle Size Range:
 - Melting Point:
 - % Volatiles:
 - Observations:
- VII. Analytical Methods:**
 - HPLC Assay:
 - TLC Assay:
 - UV/VIS Spectroscopy:
 - Synthetic Route:
 - Probable Decay Products:
- VIII. Key Dates:**
 - Bulk Scale-Up:
 - Toxicology Start Date:
 - Clinical Supplies Preparation:
 - IND Filing:
 - Phase I Testing:
- IX. Critical Development Issue(s):**

**Essential
requirement
helpful in designing
Preformulation**

DISCIPLINES



PHYSICO-CHEMICAL CHARACTERISATION

A. Physical Properties of Drug Substances

- ✓ Organoleptic Characterisation
- ✓ Bulk Characterisation
- ✓ Solubility Profile

B. Chemical Properties of Drug Substances

- ✓ Hydrolysis
- ✓ Oxidation
- ✓ Reduction
- ✓ Racemisation
- ✓ Polymerisation

A. PHYSICAL PROPERTIES OF DRUG SUBSTANCES

- ❖ The physical properties of drug molecules **can affect the structure and stability of formulations** and may also alter the bioavailability of the drugs from the dosage forms.
- ❖ Hence, physical properties of drugs are important in the dosage form design.
- ❖ There are three categories of physical properties influence dosage form design.
 - ✓ Organoleptic Characterisation
 - ✓ Bulk Characterisation
 - ✓ Solubility Profile

i) Organoleptic Characterisation

Refers to the evaluation of drug on the basis of

1. Color,
2. Odor,
3. Texture and
4. Taste.

- ❖ Product should be good in appearance.
- ❖ Colour should be eye – appealing.
- ❖ Odour and taste should be pleasant.
- ❖ Absence of impurities and should be in the purest form.

ii) Bulk Characterisation

❑ Bulk characterisation of drug molecules involves the characterisation of various solid – state properties that could change during the process development.

Variability of bulk characterisations, significantly prove subsequent events and approaches in drug development process.

Bulk Characterization includes

- Crystallinity, Amorphism, and Polymorphism physical properties
- Hygroscopicity
- Fine particle characterisation
- Density (Bulk density)
- Powder Flow Properties.

Crystallinity, Amorphism, and Polymorphism – Physical properties

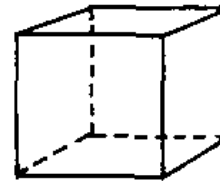
1. Crystallinity

- Crystal compounds are characterised by repetitious spacing of constituent atoms or molecules.
- Crystals can be of different shapes. E.g cubic, tetragonal, orthorhombic etc.
- The crystal habit and crystal internal structure of a drug can affect the bulk and flow properties as well as chemical stability.
- Crystal habit – outer appearance of a crystal

CRYSTAL HABIT



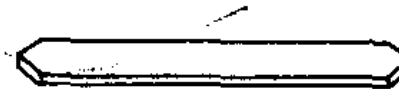
Platy



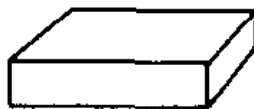
Equant or Massive



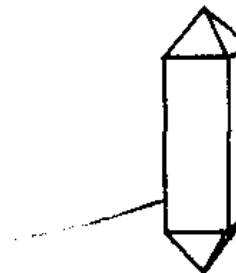
Needle or Acicular



Bladed



Tabular

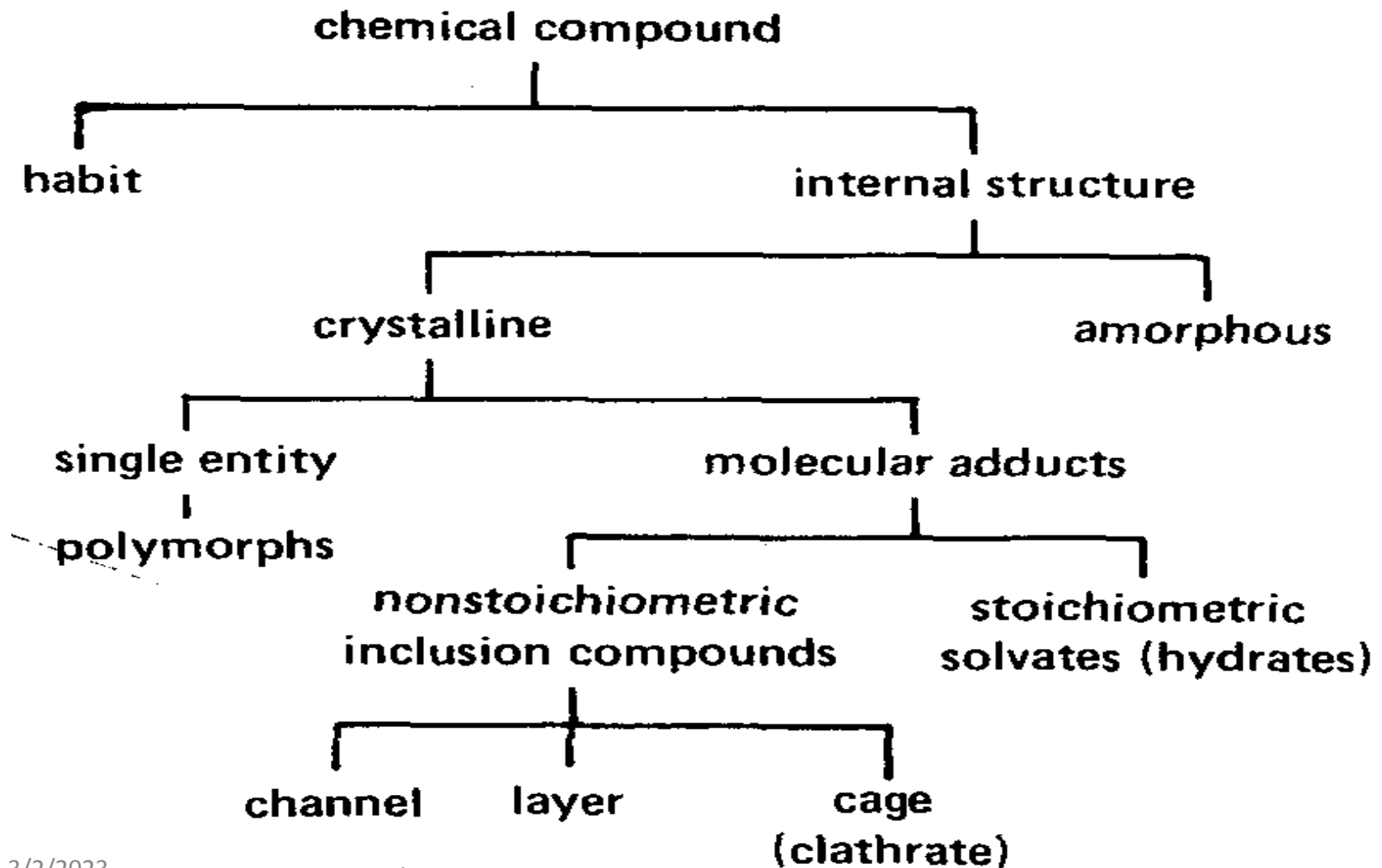


Prismatic

1. CRYSTALLINITY

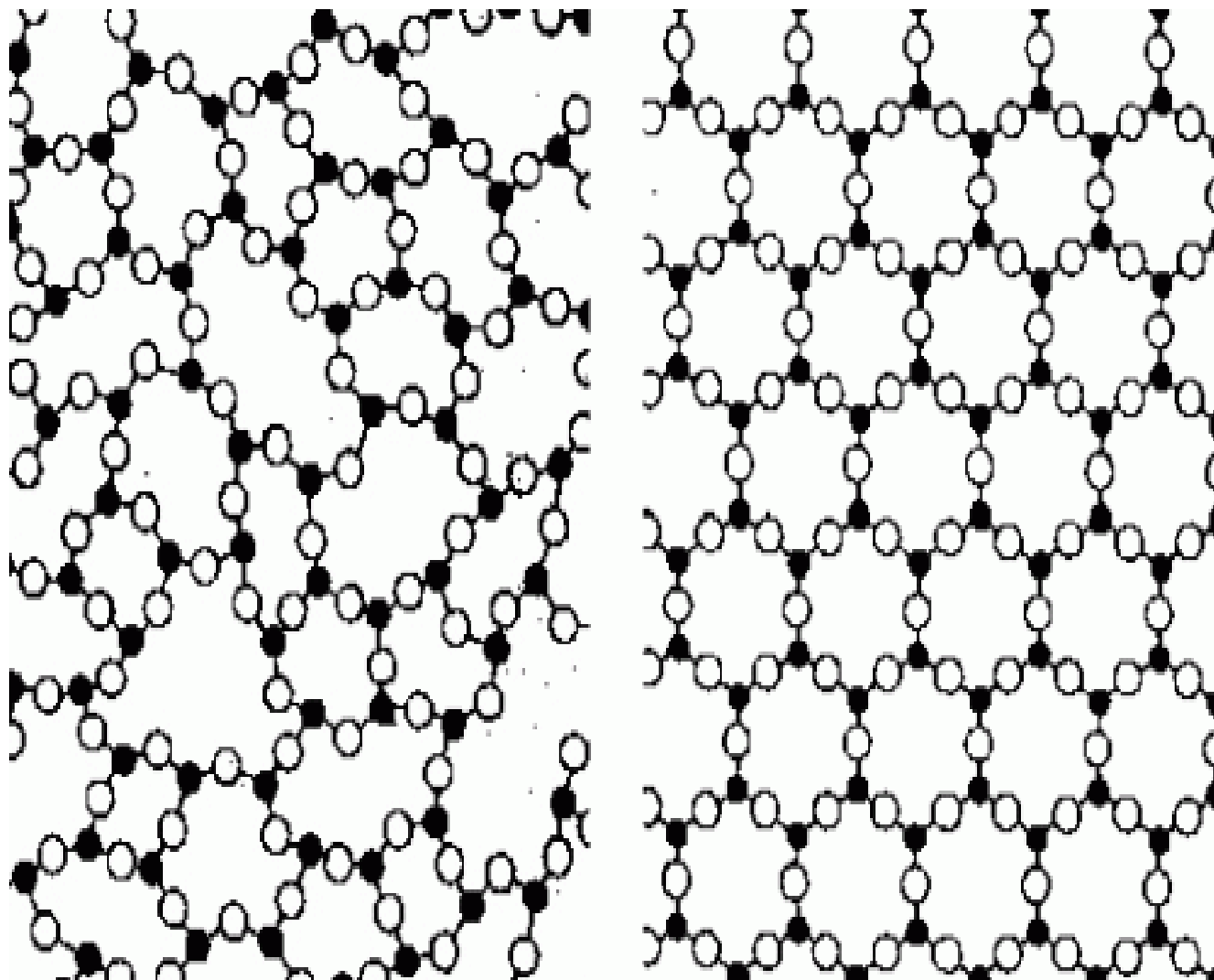
- ❖ Internal structure – molecular arrangement within the solid.
- ❖ Degree of crystallinity affects the hardness, density, transparency, and diffusion.
- ❖ Crystallinity has a greater affect on the absorption of drugs.
- ❖ Crystalline compounds may have
 - ❖ stoichiometric or
 - ❖ non – stoichiometric adduct,Where the non–stoichiometric adduct is undesirable and removed.

INTERNAL STRUCTURE



2. AMORPHISM

- ❖ Amorphous compounds are those whose atoms or **molecules are randomly placed.**
- ❖ Internal structure shows a major distinction whether the solid is crystalline or amorphous.
- ❖ Some drugs can exist in amorphous state. They are typically prepared by rapid precipitation, lyophilization.
- ❖ Such drugs **represent highest energy state**, or higher thermodynamic energy than the crystalline state.
- ❖ Amorphous form are **less stable than its crystalline state.**
- ❖ The solubility of amorphous form is **greater than its crystalline state.**
- ❖ Upon storage, amorphous solids tend to revert to more stable forms. Thermodynamic instability is a major disadvantage for developing a dosage form.



Amorphous structure of a glassy solid (left) and lattice structure of a crystalline solid (right).

2. POLY-MORPHISM

- When a substance exists in more than one crystalline form
 - **The different forms are designated as Polymorphs and this phenomenon is known as Polymorphism.**
- Polymorphs are of two types
- **Enantiotropic polymorphs** – is the one which can be reversibly changed into another form by altering the temperature or pressure.
- **Monotropic polymorphs** – is the one which is unstable at all temperatures and pressures.
- Polymorphs differ from each other respect to their physical properties like solubility, melting point, density etc.
- Depending on the stability on enantiotrops will be more stable than the other. Such stable forms have **lower energy state**, high melting point, least aqueous stability.
- Other forms are called metastable forms with the opposite properties.
- Determined by **Differential Scanning Calorimetry, X –Ray Diffraction methods.**

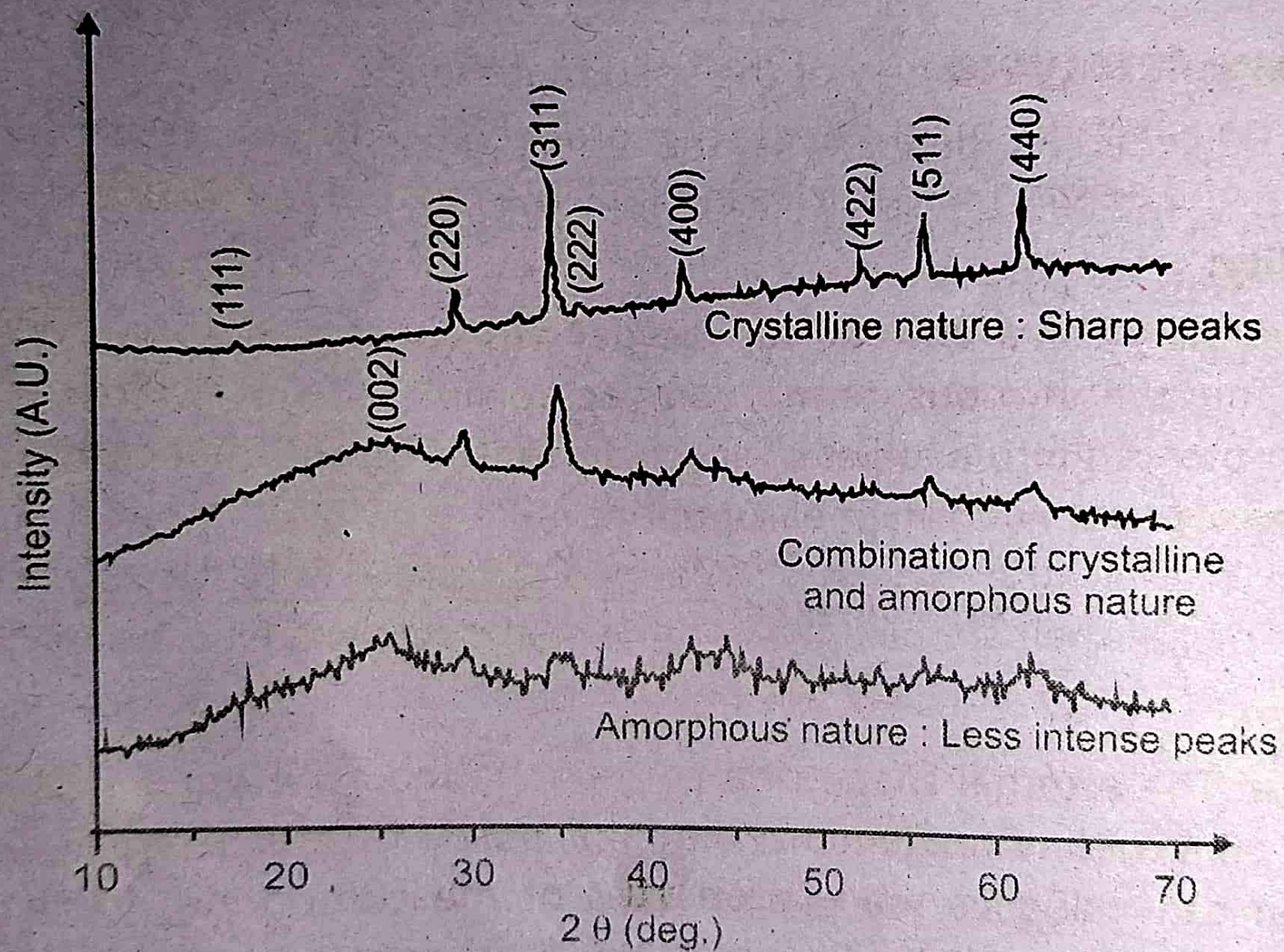


Fig. 2.4: X-Ray Diffractograms of Different Forms of Solids

Pseudo-polymorphs (Hydrate/ Solvates)

- **Pseudo-polymorphism** is also a known phenomenon in which two compounds exhibit different crystalline structures, of which one is the host of solvent molecules.
- A **hydrate** is a substance that contains water or its constituent elements.
- The chemical state of the water varies widely between different classes of hydrates, some of which were so labeled before their chemical structure was understood.

References

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The background of the slide is a dense, repeating pattern of small, light blue water droplets. Each droplet is rendered with a soft highlight and shadow, giving it a three-dimensional appearance. They are scattered across the entire frame, creating a textured, refreshing visual effect.

Thank You