आईएफटीएम विश्वविद्यालय, मुरादाबाद, उत्तर प्रदेश

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 beprocessed 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:**

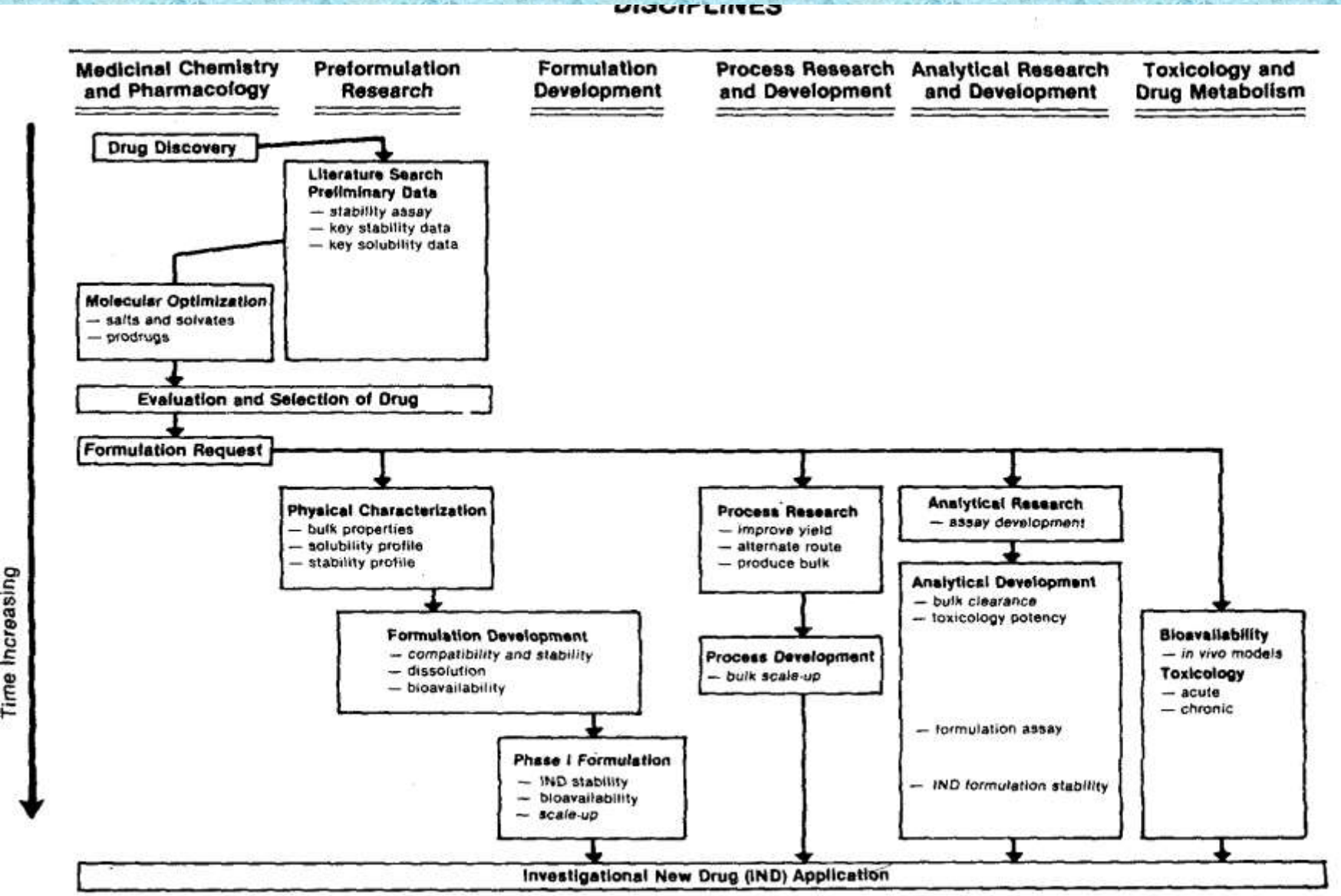
HPLC Assay:
TLC Assay:
UV/VIS Spectroscopy:
Synthetic Route:
Probable Decay Products:

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
Medicinal Chemistry and Pharmacology
Preformulation Research
Formulation Development
Process Research and Development
Analytical Research and Development
Toxicology and Drug Metabolism
Time Increasing
Drug Discovery
Literature Search
Preliminary Data
— stability assay
— key stability data
— key solubility data
Molecular Optimization
— salts and solvates
— prodrugs
Evaluation and Selection of Drug
Formulation Request
Physical Characterization
— bulk properties
— solubility profile
— stability profile
Formulation Development
— compatibility and stability
— dissolution
— bioavailability
Phase I Formulation
— IND stability
— bioavailability
— scale-up
Process Research
— improve yield
— alternate route
— produce bulk
Process Development
— bulk scale-up
Analytical Research
— assay development
Analytical Development
— bulk clearance
— toxicology potency
— formulation assay
— IND formulation stability
Bioavailability
— in vivo models
Toxicology
— acute
— chronic
Investigational New Drug (IND) Application

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

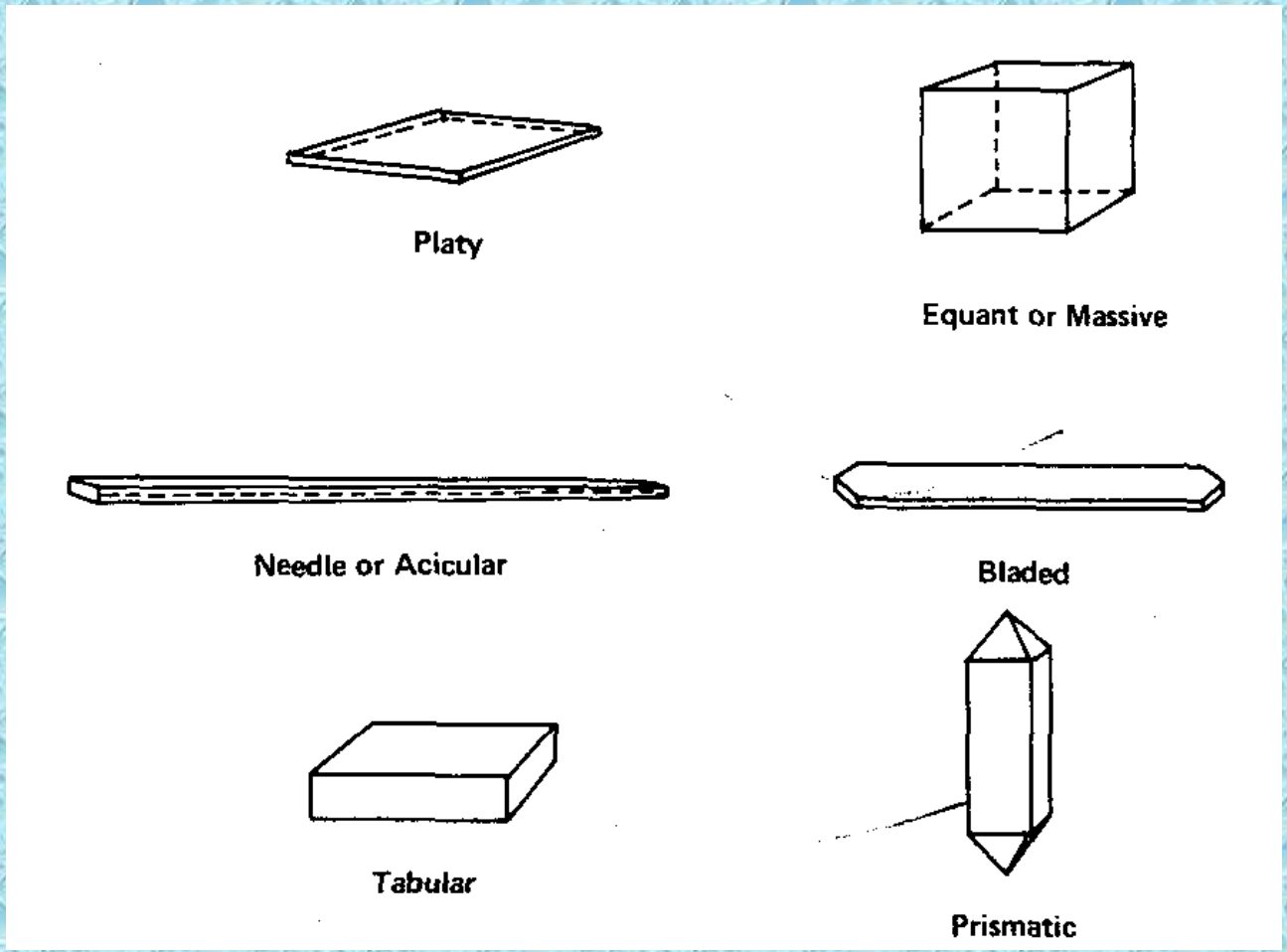
- Crystallinity, Amorphism, and Polymorphism physical properties
- Hygroscopicity
- Fine particle characterisation
- Density (Bulk density)
- Powder Flow Properties.

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

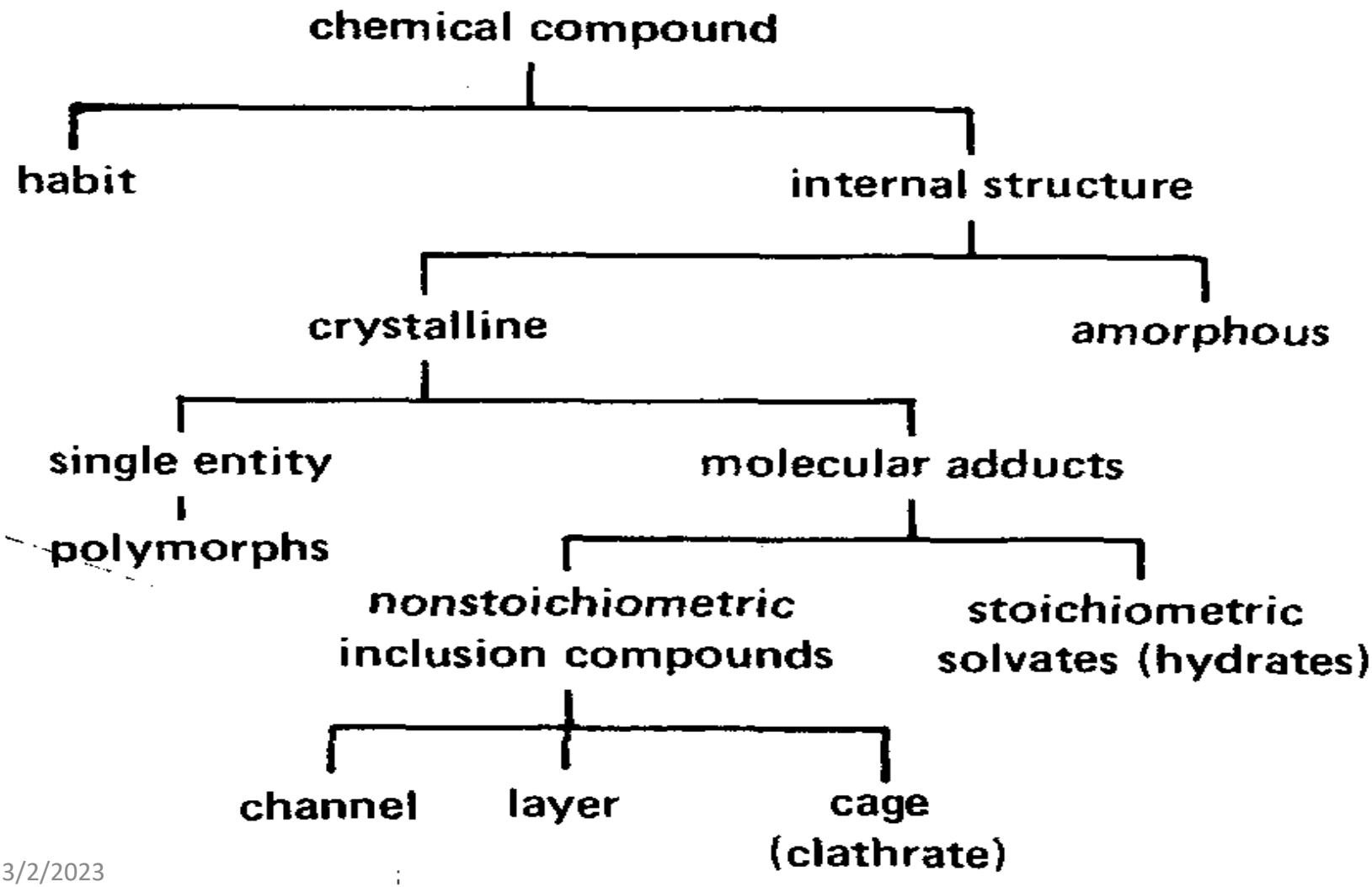


1. CRYSTALLINITY

- 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,

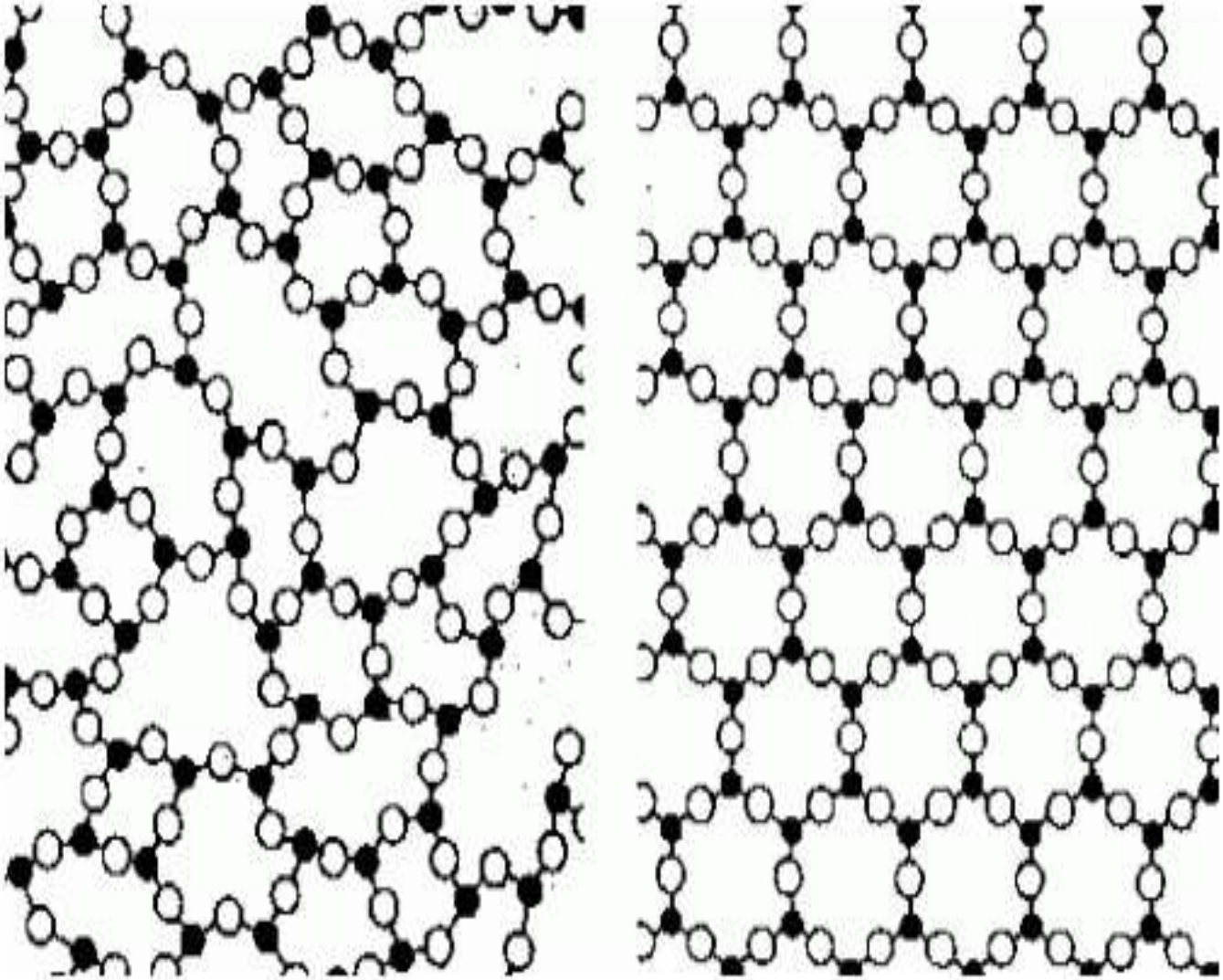
  Where the non–stoichiometric adduct is undesirable and removed.

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 theis phenomenon is known as Polymorphism.**
- Polymorphs are of two types
- **Enantiotropicpolymorphs** – 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.**

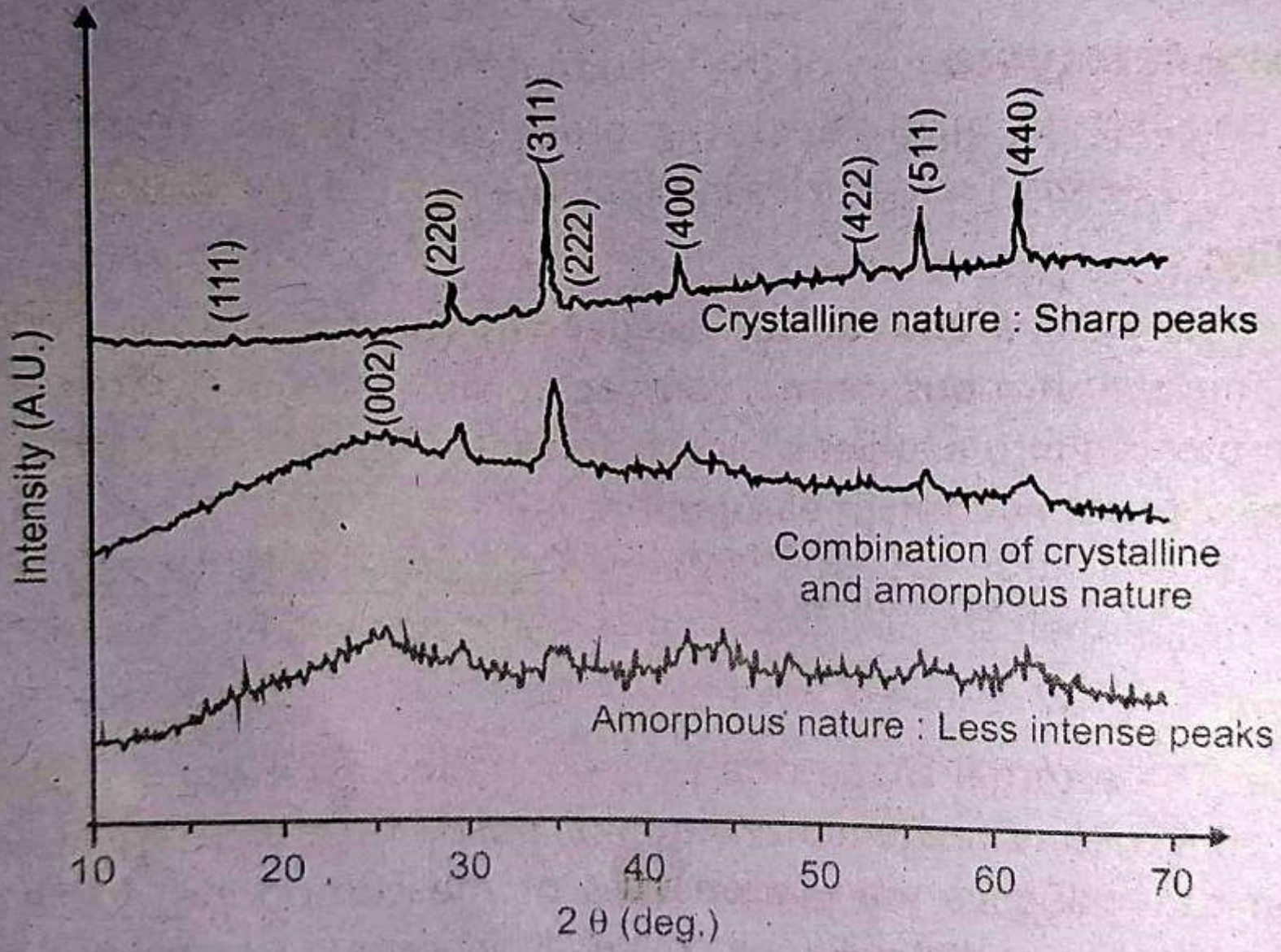


Fig. 2.4: X-Ray Diffractograms of Different Forms of Solids

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.

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Thank You