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PHYSICAL PHARMACEUTICS - I
UNIT 2

TOPIC :

- **States of Matter and properties of matter :** State of matter, changes in the state of matter, latent heats, vapour pressure, sublimation critical point, eutectic mixtures ,gases, aerosols– inhalers, relative humidity, liquid complexes, liquid crystals, glassy states, solid
  crystalline, amorphous & polymorphism.

States of Matter

- Anything that has **mass** and occupies **space** is known as **matter**.
- Matter is made up of tiny particles called **atoms** or **molecules**.
- Matter exists in **three main physical states**:
  - **Solid State**
  - **Liquid State**
  - **Gaseous State**

Solids

- Solids are substances that have a definite shape and definite volume.
- The particles in solids are closely packed, resulting in high density and low compressibility.
- Examples: Tablet, Capsule, Salt, Sugar

Liquids

- Liquids are substances that have a definite volume but no definite shape (they take the shape of the container).
- Particles in liquids have more space between them than solids, allowing fluidity and moderate compressibility.
- Examples: Water, Syrup, Milk

Gases

- Gases are substances that have neither definite shape nor definite volume.
- Gas particles are far apart, resulting in low density, high compressibility, and high diffusion.
- Examples: Oxygen, Nitrogen, Aerosols

Comparison of Properties of Solid, Liquid, and Gas

Property	Solid	Liquid	Gas
Shape	Definite	Indefinite	Indefinite
Volume	Definite	Definite	Indefinite
Intermolecular Space	Least	Intermediate	Maximum
Kinetic Energy	Least	Intermediate	Highest
Compressibility	Very low	Slight	High
Diffusion Rate	Negligible	Moderate	Fast
Rigidity	High	Medium	None
Density	Highest	Intermediate	Lowest
Flow Property	Cannot flow	Can flow	Flows freely

Changes in State of Matter

- Matter can change from one state to another by absorbing or releasing heat.
- These changes are physical changes and are reversible in most cases.

Processes of Change:

Process	From → To	Energy Involved
Melting	Solid → Liquid	Heat absorbed
Freezing	Liquid → Solid	Heat released
Evaporation/Boiling	Liquid → Gas	Heat absorbed
Condensation	Gas → Liquid	Heat released
Sublimation	Solid → Gas directly	Heat absorbed
Deposition	Gas → Solid directly	Heat released

Latent Heat

- The term Latent Heat was introduced by Joseph Black, a British chemist, in 1762.
- Latent Heat is defined as the amount of heat energy absorbed or released by a substance during a change of its physical state (phase) without any change in temperature.
- It is called "latent" (meaning hidden) because the heat goes into changing the state of the substance and does not raise its temperature.

Explanation of Latent Heat

- Consider a block of ice at 0°C.
- When heat is supplied to the ice:
  - The temperature of the ice does not increase immediately.
  - Instead, the energy is used to break the bonds between the ice molecules to convert it into liquid water.
  - Once all ice is converted into water, then only the temperature starts rising.
- This absorbed heat used in changing the state (solid to liquid) without changing the temperature is known as Latent Heat.

Types of Latent Heat

There are two main types of latent heat:

1. Latent Heat of Fusion
2. Latent Heat of Vaporization

1. Latent Heat of Fusion

- It is the amount of heat energy required to convert 1 gram of a solid into liquid at its melting point, without changing its temperature.
- Also applicable when liquid changes to solid (heat is released).
- For water:
  Latent Heat of Fusion = 334 J/g
  (i.e., 334 joules of energy is needed to convert 1 gram of ice at 0°C into water at 0°C)

2. Latent Heat of Vaporization

- It is the amount of heat energy required to convert 1 gram of a liquid into gas at its boiling point, without changing its temperature.
- Also applicable when gas changes back to liquid (heat is released).
- For water:
  Latent Heat of Vaporization = approx. 2250 J/g
  (i.e., 2250 joules of energy is needed to convert 1 gram of water at 100°C into steam at 100°C)

Importance of Latent Heat

- Helps in understanding phenomena like:
  - Why ice keeps drinks cold for a long time.
  - Why sweating cools the body (evaporation absorbs latent heat).
- Used in pharmaceutical applications like freeze-drying, aerosols, and temperature control of drug storage.

Vapour Pressure

- Vapour pressure is defined as the pressure exerted by the vapour molecules when a liquid is placed in a closed container and a dynamic equilibrium is established between vapourization and condensation.

Explanation

- When a liquid is placed in a closed container, some molecules at the surface of the liquid gain enough kinetic energy to escape into the space above the liquid — this process is called vapourization.
- As more molecules escape, their concentration in the air increases.
- Eventually, some of these vapour molecules lose energy and return to the liquid — this is known as condensation.
- After some time, a state of dynamic equilibrium is established where the rate of vapourization = rate of condensation.
- At this equilibrium, the pressure exerted by the vapour molecules on the liquid surface is called the Vapour Pressure of that liquid.

Dynamic Equilibrium Representation

Rate of Vapourization ⇌ Rate of Condensation

- At equilibrium, the amount of liquid and vapour remains constant, but molecules continue to change states.

Factors Affecting Vapour Pressure

1. **Nature of the Liquid:**
   - Liquids with weak intermolecular forces (like alcohol or ether) have higher vapour pressure.
   - Liquids with strong intermolecular forces (like water or glycerol) have lower vapour pressure.
2. **Temperature:**
   - As temperature increases, the kinetic energy of molecules increases, resulting in higher vapour pressure.
   - Vapour pressure rises exponentially with temperature.
3. **Intermolecular Forces:**
   - Stronger forces between molecules (e.g., hydrogen bonding) lower the vapour pressure.
   - Weaker forces result in higher vapour pressure because molecules escape more easily.

Eutectic Mixture

- The term "Eutectic" is derived from the Greek word eutektos, which means "easily melted".
- A eutectic mixture is a mixture of two or more solid substances that, when combined in a particular proportion, results in a mixture having a melting point lower than the melting point of each individual component.
- This behavior is due to the interference of crystal lattice formation when the components are mixed, leading to a depression in melting point.

Key Concept

- When components A and B are mixed:
  - The eutectic point is the lowest possible melting point for that specific combination.
  - At this point, both components melt simultaneously to form a liquid.

Example of Eutectic Mixtures

- Thymol + Camphor
- Menthol + Camphor
- Salol + Beta-naphthol

When these components are mixed in specific ratios, they form a liquid phase at room temperature, even though each is a solid individually.

Eutectic Temperature and Composition:

- The eutectic temperature is the lowest temperature at which the eutectic mixture can exist as a liquid.
- Below the eutectic temperature, the mixture exists in a solid state.
- Above the eutectic temperature, the components form a liquid melt.

Factors Affecting Eutectic Mixture Formation

1. **Ratio of Components:**
    - Only specific ratios lead to eutectic behavior.
2. **Presence of Impurities:**
    - Impurities can disturb crystal formation, affecting melting behavior and stability.
3. **Particle Size and Surface Area:**
    - Finer particles mix more intimately, which enhances eutectic formation.
4. **Mixing Method:**
    - Uniform and thorough mixing helps in achieving a proper eutectic system.

Applications Of Eutectic Mixtures In Pharmaceutics

1. **In Drug Formulation:**
    - Eutectic mixtures are used to enhance solubility, dissolution rate, and bioavailability of poorly soluble drugs.
2. **To Prevent Incompatibility:**
    - Incompatible drugs can be formulated in eutectic mixtures to improve stability.
3. **In Topical Preparations:**
    - Used in ointments or creams where melting at body temperature is desired.

Gases

- Gases are substances that have neither a fixed shape nor a fixed volume.
- They occupy the entire space available in the container.
- Gas molecules possess very weak or negligible intermolecular forces, allowing them to move freely in all directions.
- Due to high kinetic energy, gas particles are in constant random motion.

Characteristics of Gases

- No definite shape or volume.
- Highly compressible.
- Low density compared to solids and liquids.
- High diffusion rate.
- Exert pressure on the walls of the container due to continuous molecular collisions.

Parameters of Gases

There are 4 major parameters that describe the physical behavior of gases:

Parameter	Symbol	Unit	Description
Volume	V	Litres (L) or m^3	Space occupied by the gas
Pressure	P	atm, Pa, mmHg	Force exerted by gas molecules per unit area
Temperature	T	Kelvin (K)	Measure of kinetic energy of gas molecules
Number of Moles	n	moles (mol)	Amount of gas particles present

GAS LAWS

➢ Gas laws explain the relationships between the four gas parameters. The major gas laws are:

1. Boyle's Law (Pressure–Volume Relationship):

- **Statement:** At constant temperature, the volume of a given mass of gas is inversely proportional to its pressure.

$$P \propto \frac{1}{V} \quad \text{(when T and n are constant)}$$

$$P_1V_1 = P_2V_2$$

2. Charles's Law (Volume–Temperature Relationship):

- **Statement:** At constant pressure, the volume of a given mass of gas is directly proportional to its absolute temperature (in Kelvin).

$$V \propto T \quad \text{(when P and n are constant)}$$

$$\frac{V_1}{T_1} = \frac{V_2}{T_2}$$

3. Gay-Lussac's Law (Pressure–Temperature Relationship):

- **Statement:** At constant volume, the pressure of a given mass of gas is directly proportional to its absolute temperature.

$$P \propto T \quad \text{(when V and n are constant)}$$

$$\frac{P_1}{T_1} = \frac{P_2}{T_2}$$

4. Avogadro's Law (Volume–Moles Relationship):

- **Statement:** At constant temperature and pressure, equal volumes of all gases contain equal number of molecules.

$$V \propto n \quad \text{(when T and P are constant)}$$

$$\frac{V_1}{n_1} = \frac{V_2}{n_2}$$

5. Ideal Gas Law (Combined Gas Law):

- It combines all the individual gas laws into a single equation:

$$PV = nRT$$

Where:

- P = Pressure
- V = Volume
- n = Number of moles
- R = Universal gas constant = 0.0821 L·atm/mol·K
- T = Temperature in Kelvin

Aerosols

- An Aerosol is a pressurized dosage form in which the active pharmaceutical ingredient (API) is dissolved or suspended in a propellant (gas or liquid) and packaged in a suitable container fitted with a valve and actuator.
- Upon activation, the drug is released as a fine mist, spray, or foam.

Applications of Aerosols

- **Pharmaceutical Products:**
    - Pulmonary sprays (e.g., for asthma and COPD)
    - Muscle relaxant sprays
    - Topical anesthetics
    - Nasal sprays
- **Non-pharmaceutical Products:**
    - Deodorants (Deo's)
    - Insecticides
    - Room fresheners
    - Paint and color sprays

Components of Aerosol System

A typical aerosol system consists of the following main components:

Component	Function
1. Can/Container	Holds the formulation and withstands pressure
2. Valve	Controls the release of the contents in a measured amount
3. Actuator	The part pressed by the user to activate the valve
4. Dip Tube	Carries the liquid formulation from the bottom of the can to the valve
5. Propellant	The gas or liquefied gas that helps in expelling the product as a spray
6. Formulation (Drug + Ingredients)	Contains the active drug, solvents, surfactants, etc.

Advantages of Aerosols

- ✓ Allows direct application of the drug to the affected area.
- ✓ Rapid onset of action, especially in respiratory diseases.
- ✓ Convenient and easy to use.
- ✓ Sterile until used.
- ✓ Reduced systemic side effects (in topical/pulmonary use).

Disadvantages of Aerosols

- Expensive compared to conventional dosage forms.
- May cause allergic reactions in some individuals (due to propellants).
- Disposal issues due to pressurized containers (environmental concern).
- Risk of misuse or overuse in certain cases.

Inhalers

- ➢ An Inhaler is a medical device designed to deliver medications directly into the lungs through inhalation.
- ➢ It is commonly used for the treatment of asthma, COPD (Chronic Obstructive Pulmonary Disease), and other respiratory disorders.

Advantage of Inhalers

- Fast onset of action due to direct delivery to the lungs.
- Requires lower doses compared to oral medications.
- Minimizes systemic side effects.
- Portable and easy to use.

Types of Inhalers

There are three main types of inhalers based on the mechanism of drug delivery:

1. Metered Dose Inhalers (MDIs):

- Also called pressurized inhalers.
- Deliver a measured (metered) amount of medication in aerosol form.
- Requires coordination between actuation and inhalation.
- Often used with spacers to make usage easier.

Example: Salbutamol MDI

2. Dry Powder Inhalers (DPIs):

- Contain medication in the form of a dry powder.
- The inhalation effort of the patient helps in drawing the drug into the lungs.
- No propellant is used.
- Easier to use for patients with good lung capacity.

Example: Rotahaler with Salmeterol

3. Soft Mist Inhalers (SMIs):

- Deliver a slow-moving mist that stays longer in the air, allowing easier inhalation.
- Does not require strong inhalation effort, making it suitable for elderly or weak patients.
- Example: Respimat Inhaler

Inhaler Usage Tips

- Shake well before use (for MDIs).
- Exhale before inhaling medication.
- Hold breath for 5–10 seconds after inhaling.
- Rinse mouth after using steroid-based inhalers to prevent fungal infections.

Relative Humidity

- Humidity refers to the amount of water vapour present in the air.
- Relative Humidity is defined as the ratio of the amount of water vapour actually present in the air to the maximum amount of water vapour that the air can hold at the same temperature, expressed as a percentage.

$$\text{Relative Humidity (RH)} = \left(\frac{\text{Actual Water Vapour in Air}}{\text{Maximum Water Vapour Air Can Hold at That Temperature}}\right) \times 100$$

Explanation

- Warm air can hold more water vapour than cold air.
- When air holds as much moisture as it can at a given temperature, the relative humidity is 100%.
- If the air contains half of the maximum vapour, the RH is 50%.

Example

- At 30°C, suppose air can hold a maximum of 30 g of water vapour per m³, but currently it contains 15 g.
- Then,

$$\text{RH} = \left(\frac{15}{30}\right) \times 100 = 50\%$$

Importance of Relative Humidity In Pharmaceutics:

- **Drug stability:** High RH can cause moisture-sensitive drugs to degrade.
- **Packaging design:** Helps in selecting moisture-proof packaging.
- **Storage:** Proper RH levels are maintained in pharmaceutical warehouses (usually less than 60%).

- **Manufacturing:** Ensures proper drying of tablets and powder flow during production.

Sublimation & Critical Point

Sublimation

- Sublimation is the process in which a solid changes directly into gas without passing through the liquid state.

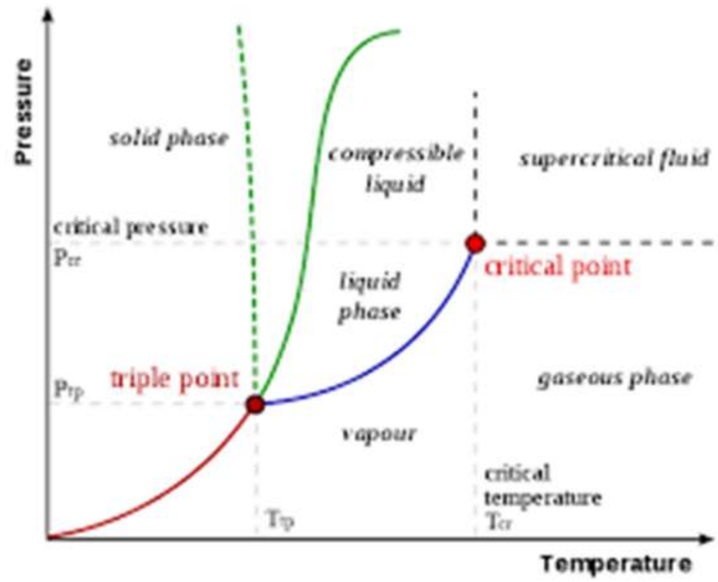
Solid→Gas(without becoming liquid)\text{Solid} \rightarrow \text{Gas} \quad (\text{without becoming liquid})Solid→Gas(without becoming liquid)

- It occurs when the vapor pressure of a solid is high enough to form a gas directly at certain temperature and pressure conditions.
- **Examples:**
    - Dry Ice (Solid CO_2)
    - Camphor
    - Iodine
    - Naphthalene balls

Critical Point

- The Critical Point is the temperature and pressure at which the liquid and gas phases of a substance become indistinguishable, forming a supercritical fluid.
- A supercritical fluid behaves partly like a liquid and partly like a gas — it can dissolve substances like a liquid and flow like a gas.
- On a phase diagram, the critical point is the end point of the liquid–gas boundary line.

PHASE DIAGRAM OVERVIEW:



The diagram typically includes:

- Solid region
- Liquid region
- Gas (vapour) region
- Triple point: Where solid, liquid, and gas coexist in equilibrium.
- Critical point: Beyond which there is no distinction between liquid and gas.

Triple Point

- The triple point is the unique temperature and pressure at which a substance exists in equilibrium in all three phases — solid, liquid, and gas.
- Each substance has its own specific triple point.

Sublimation Critical Point

- The Sublimation Critical Point refers to the specific temperature and pressure at which a substance can undergo sublimation, i.e., convert directly from solid to gas without passing through the liquid state.
- This is below the triple point on the phase diagram.
- Example: Dry Ice (Solid CO_2)
    - Sublimes at –78.5°C (194.65 K) at 1 atm pressure.

- There is no liquid phase for CO_2 at normal atmospheric pressure — it directly becomes gas.

Importance In Pharmaceutics

- ❖ Used in lyophilization (freeze-drying) to prepare thermolabile drugs.
- ❖ Helps in the formulation of inhalable powders.
- ❖ Applied in sublimable ointment bases and storage techniques for moisture-sensitive drugs.

Liquid Complexes

- The term Liquid Complexes, also referred to as Complex Fluids, describes fluids (liquids or gases) that have dispersed particles or components of another phase (solid, liquid, or gas) suspended within them.
- These systems are often binary mixtures showing coexistence of two or more phases in a single fluid system.

Key Characteristics

- Appear fluid-like but show complex structural behavior.
- May exhibit properties of both fluids and solids, depending on the nature of the dispersed phase.
- Their internal structure can be affected by external forces like stress, temperature, or electric fields.

Types of Liquid Complexes

Type	Description	Example
1. Solid–Liquid Complexes	Suspension of solid particles in a liquid medium	Pharmaceutical suspensions
2. Solid–Gas Complexes	Solid particles dispersed in gas	Aerosols
3. Liquid–Gas Complexes	Gas bubbles dispersed in a liquid	Foams
4. Liquid–Liquid Complexes	Immiscible liquids dispersed within one another	Emulsions

Properties of Liquid Complexes

1. **Inherently Disordered:**
   - The molecular arrangement is non-uniform and lacks long-range order.
2. **Strongly Heterogeneous:**
   - These mixtures contain components of different phases or states, creating non-uniform composition throughout the fluid.
3. **Non-Newtonian Behavior:**
   - They often do not follow Newton's law of viscosity — viscosity changes under applied stress or shear.
4. **Unusual Mechanical Responses:**
   - They may exhibit shear thinning, thickening, or viscoelastic behavior when external force is applied.
5. **Phase Instability:**
   - Over time, separation of phases can occur if stabilizers are not used (e.g., emulsifiers, surfactants).

Pharmaceutical Importance

- Used in drug formulations like :
  - Suspensions, emulsions, aerosols, and foams.
- Enhance solubility and bioavailability of poorly water-soluble drugs.
- Allow for controlled release, targeted delivery, and topical application.
- Critical in designing cosmetics, creams, and inhalable therapies.

Liquid Crystals

Liquid crystals are a distinct state of matter that exhibit properties between those of conventional liquids and solid crystals.
They are also known as:

- Mesophases
- Fourth state of matter

In liquid crystals, molecules have some degree of ordering (like solids) but also flow (like liquids).

State of Matter Transition

SOLID → LIQUID CRYSTAL → LIQUID

Classification of Liquid Crystals

Based on the orientation and position of molecules, liquid crystals are classified into three main types:

1. **Nematic Phase:**
   - Molecules are aligned in the same direction (parallel), but their positions are random.
   - Least ordered phase among liquid crystals.
   - Common in LCD (Liquid Crystal Display) screens.

2. **Smectic Phase:**
   - Molecules are aligned parallel and arranged in distinct layers.
   - Shows more order than the nematic phase.
   - Layers can slide over one another like a soap film.

3. **Cholesteric Phase (Chiral Nematic):**
   - Molecules are arranged in layers, and the orientation of molecules rotates slightly in each layer, forming a helical pattern.
   - Found in temperature-sensitive materials and color-changing paints.

Properties of Liquid Crystals

1. **Flowability:**
   - Like liquids, they can flow easily.
2. **Ordered Molecular Arrangement:**
   - Similar to crystals, they exhibit directional ordering.
3. **Surface Tension:**
   - They possess surface tension like liquids.
4. **Anisotropic Nature:**
   - Their physical properties (e.g., refractive index, conductivity) vary with direction.
5. **Responsive to External Stimuli:**
   - Their structure changes with temperature, electric field, or magnetic field.

Applications of Liquid Crystals

Application Area	Examples
Display Technology	LCDs in TVs, calculators, digital watches
Temperature Sensors	Color-changing thermometers and baby bath thermometers
Pharmaceuticals	Drug delivery systems, especially transdermal patches
Cosmetics	Used in lipsticks, make-up removers, moisturizers for better texture and stability
Smart Coatings	Thermochromic paints, smart windows

GLASSY STATE

- The Glassy State, also referred to as a supercooled liquid, is a solid-like state of matter where the material appears solid but has an amorphous (non-crystalline) internal structure.
- Unlike crystals, molecules in the glassy state are randomly arranged—similar to a liquid—but the material behaves mechanically like a solid.

Formation of Glassy State

- Formed when a liquid is cooled rapidly (quenched) from its molten state without giving the molecules enough time to form a crystalline lattice.
- The substance bypasses crystallization and becomes an amorphous solid.

Example : Molten silica (SiO_2) cooled rapidly becomes glass.

Characteristics of Glassy State:

Property	Description
Amorphous Nature	Molecules are arranged randomly, not in a definite pattern (unlike crystals).
Transparency	Often clear or see-through, especially in glass or plastics.
Solid Appearance	Appears rigid and solid to the eye and touch.
Brittleness	Breaks easily under stress—does not bend or deform like true solids.
Supercooled Liquid	Though solid in appearance, it behaves like an extremely slow-flowing liquid.
Glass Transition Temperature (Tg)	Has a specific temperature below which the material becomes hard and brittle.

Examples of Materials In Glassy State

- Glass (SiO_2)
- Polymers (like polystyrene or PMMA)
- Sugar-based syrups (on rapid cooling)
- Certain pharmaceutical preparations (e.g., amorphous drug formulations)

Applications In Pharmacy

- **Amorphous Drug Forms** – Many poorly water-soluble drugs are converted to glassy (amorphous) forms to enhance solubility and bioavailability.
- **Stabilization of Biologicals** – Glassy state is used in freeze-drying or lyophilization to stabilize protein drugs.
- **Packaging** – Glass containers are inert and ideal for storing sensitive medications.

Properties of Amorphous Solids

Property	Description
Order	Only short-range order (no regular long-range structure)
Melting Point	Do not have a sharp melting point; melt over a range
Cleavage	Breaks irregularly
Isotropy	Properties are the same in all directions
Stability	Less thermodynamically stable than crystalline forms

Crystalline vs. Amorphous Solids

Feature	Crystalline Solids	Amorphous Solids
Particle Arrangement	Regular, long-range order	Irregular, short-range order
Melting Point	Sharp	Gradual over a range
Anisotropy	Yes	No (Isotropic)
Cleavage	Definite planes	Irregular
Stability	More stable	Less stable
Examples	NaCl, Quartz, Iron	Glass, Plastic, Rubber

Polymorphism

The word *Polymorphism* is derived from the Greek words:

- "Poly" = many
- "Morph" = forms

When a substance exists in more than one crystalline form, and each form has different physical properties, these forms are called polymorphs.
The phenomenon by which a substance can exist in more than one crystalline form is called Polymorphism.
Polymorphism in elements is specifically known as Allotropy.

Key Point:

- Polymorphs have the same chemical composition but different physical properties due to different structural arrangements of atoms or molecules.

  Examples of Polymorphic Substances:

  - **Carbon** – diamond and graphite
  - **Sulphur** – monoclinic and rhombic forms
  - **Phosphorus** – white, red, and black phosphorus

Types of Polymorphs

Polymorphs are generally classified into two types:

1. Enantiotropic Polymorphs

- In this type, one form can be reversibly transformed into another at a specific transition temperature.
- The transformation is reversible.
- Example: Sulphur
  - Exists as monoclinic and rhombic sulphur.
  - These two forms can convert into each other at a transition point.

Hence, Sulphur is an Enantiotropic Polymorph.

2. Monotropic Polymorphs

- In this case, one polymorphic form is stable, and the other can irreversibly convert into the stable form.
- The transformation is not reversible under normal conditions.
- Example: Carbon
  - Exists as diamond and graphite.
  - Diamond can convert into graphite at high temperature and pressure, but graphite does not revert to diamond.

Hence, Carbon is an example of a Monotropic Polymorph.