

Unit II

States of matter

- Matter is the “stuff” of the universe — the atoms, molecules and ions that make-up all physical substances.
- Matter is anything that has mass and takes up space. There are five known phases, or states, of matter: solids, liquids, gases, plasma (when gas is heated positive and negative particles) and Bose-Einstein condensates (formed when a gas of boson at low densities is cooled to temperature very close to zero)
- The main difference in the structures of each state is in the densities of the particles.
- Adding energy to matter causes a physical change causing matter to move from one state to another.
- For example, adding thermal energy (heat) to liquid water causes it to become steam or vapour (a gas).
- Taking away energy also causes physical change, such as when liquid water becomes ice (a solid) when heat is removed.
- These changes in states of matter and their inherent properties are studied and are applied in various area of pharmacy.

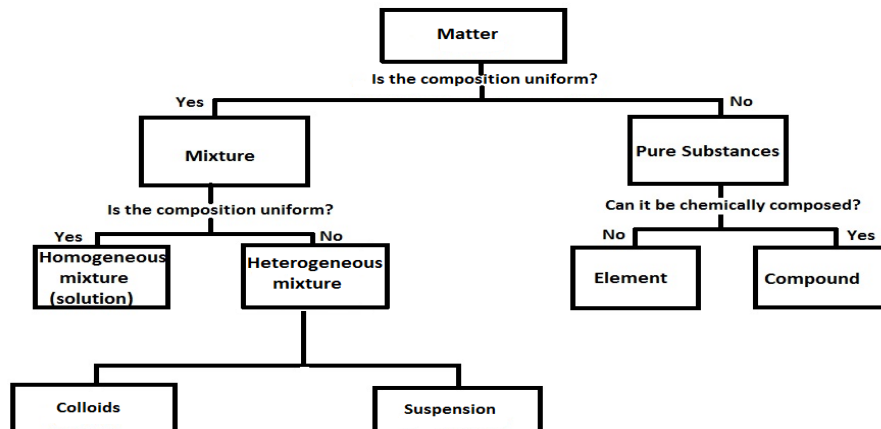


Figure: Classification of matter

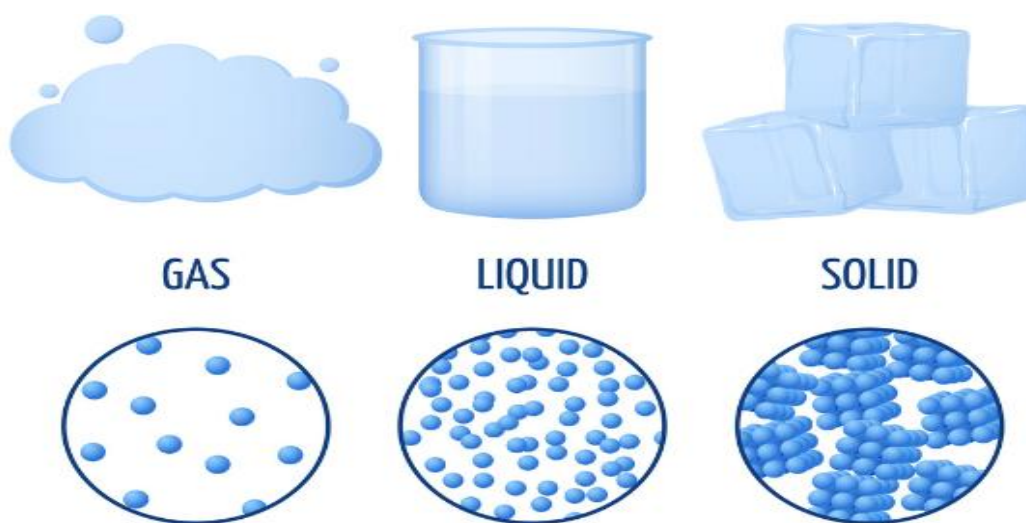


Figure: Three states of matter

- A substance is a form of matter that has a constant composition.
- Physicochemical properties of a substance are dependent on the organizational arrangement of its constituent atoms. For example, n-butane has the same chemical formula as iso-butane, C_4H_{10} .
- Physical properties namely; boiling point, melting point and relative density of both these compounds are given in Table.

Table: Physical Properties for n-butane and iso-butane

Physical Properties	n-butane	iso-butane
Boiling point	0 °C	0 °C
Melting point	- 138 °C	- 159 °C
Relative density at -20°C	0.622 g/mL	0.604 g/mL

- Vapour pressures of these compounds at a temperature and their chemical properties like reactivity differ due to **different arrangement of the same atoms in each molecule.**
- They have different structural formulas as n-butane: $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_3$ and iso-butane: $\text{CH}_3\text{-CH}(\text{CH}_3)\text{-CH}_3$ and thus the **physicochemical property of substance vary with structural arrangement.**

Table: Properties of Solid, Liquid and Gaseous State

Solid	Liquid	Gas
Retains volume and shape.	Assumes the shape of part of the container it occupies.	Assumes the shape and volume of container.
Particles are rigid and locked into place.	Particles can move/slide past one another.	Particles (molecules, atoms, ions) can move past one another.

A little free space exists between molecules.	A little free space exists between molecules.	Lots of free space exists between molecules.
Do not flow easily.	Flows easily.	Flows easily.
Not easily compressible.	Not easily compressible.	Easily compressible.

Mixture:

- A combination of two or more substances is known as mixture, which may or may not retain original physicochemical properties of its constituent components.
- There are two types of mixture namely;
 - ✓ Homogeneous mixture
 - ✓ Heterogeneous mixture

Homogenous Mixture:

- In homogenous mixture of solid and liquid the chemical and physical properties of individual components cannot be determined by any single instrumental method of analysis.
- Depending upon temperature substances exist in different states.
- For example, Aspirin below 135 °C it exists in solid crystalline form whereas above this temperature it exists in liquid form.
- Dissolving aspirin crystals in water makes aqueous aspirin solution. Water destroys the intermolecular forces between the aspirin molecules that exist as crystalline arrangement during the process of solution formation.
- In the formation of a molecular dispersion there must be some mutual interaction between solute and solvent.

- Thus, the properties of the individual components of the mixture get changed.
- All the physical properties of aspirin are changed upon interaction with water.
- Similarly, the properties of water are also get changed by the presence of the aspirin.
- Another physical property called absorption of electromagnetic radiation is changed due to homogeneous mixing.
- The chemical composition of a homogeneous mixture is always same throughout.
- Some examples of solid, liquid and gas pharmaceutical homogeneous mixtures are: **suppositories** composed of a mixture of polyethylene glycols (PEG 8000 = 40 % and PEG400 = 60 %) prepared by the melting and congealing at room temperature, **Simple Syrup** (85 % w/w or 66.8 % w/v) prepared by dissolving sucrose in water and **general anaesthesia** prepared as mixture of nitrous oxide gas with oxygen (80:20 v/v).

Heterogeneous Mixture:

- A heterogeneous mixture is one in which the individual components of the mixture retains their original physicochemical properties.
- The composition of a heterogeneous mixture may or may not be uniform throughout.
- The commonest example of heterogeneous liquid mixture is pharmaceutical suspension.
- Suspensions are liquids in which the insoluble drugs are present in the fine state and are somewhat uniformly dispersed in aqueous media.

- Kinetic forces exerted by the water molecules on the suspended drug molecules are primarily responsible for their suspension in solvent.
- The larger particles are more difficult to keep uniformly suspended in the water.
- Since the drug solubility is less, the physicochemical properties of drug and water in pharmaceutical suspensions remain practically intact.
- By means of physical methods components of homogeneous and heterogeneous mixtures can be separated and recovered as pure substances.
- However, for homogeneous mixtures great care need to be taken to recover pure components.

Examples:

1. Water present in simple syrup can be removed by boiling syrup and condensing generated vapours to get back pure water leaving behind the pure dry sugar powder. The sugar is recovered in a pure form, but not in its original, crystalline state.

2. A tablet prepared by direct compression of a drug and other excipients such as lactose, polyvinyl pyrrolidone (PVP) and magnesium stearate is an example of a heterogeneous solid mixture.

- Lactose powder tries to remain as a separate entity from the magnesium stearate and the solid drug.
- For the excipients to exert its effect in the tablet, they must retain their distinct identity along with their physicochemical properties within the powder mixture.
- PVP is the disintegrant and its swelling property facilitates disintegration of tablet in dissolution media. Interaction of PVP with the drug or with any of the other excipients may change or even neutralize its disintegration property.

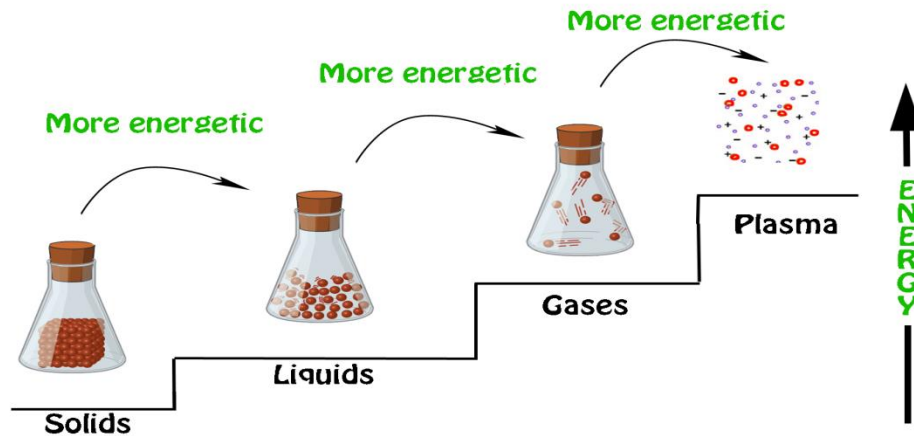
- Similarly, interaction of magnesium stearate, a lubricant, with other excipients may eliminate its lubricant properties.
- But most importantly, active drug-excipient interactions that are not expected could lead to product instability, ineffective therapy or sometimes toxicity.

3. The carbonate salts, for example, is commonly used in effervescent tablets that may cause hydrolysis of an ester drug in the presence of moisture.

- Similarly, interaction of the drug with excipients may lead to complex formation, which may have reduced solubility that may affect drug performance.

Changes in the state of matter:

- In the solid-state particles are held near by intermolecular, interatomic or ionic forces therefore the particles of solid oscillate about fixed position.
- As the temperature of solid is increased, the particles acquire enough energy to breakdown the ordered arrangement of the lattice and pass in to the liquid form.
- On further application of energy by increasing temperature, liquid molecules pass in to the gaseous state.



As you go from solids, to liquids, to gases, and finally to plasma, the energy levels of the particles are **increasing**

Figure: Change of state on increasing temperature

Freezing:

Freezing is a phase transition in which a liquid turns into a solid when its temperature is lowered below its freezing point.

Melting:

Melting, or fusion, is a physical process that results in the phase transition of a substance from a solid to a liquid. This occurs when the internal energy of the solid increases, typically by the application of heat or pressure, which increases the substance's temperature to the melting point.

Deposition:

Deposition is a thermodynamic process, a phase transition in which gas transforms into solid without passing through the liquid phase. The reverse of deposition is sublimation and hence sometimes deposition is called desublimation. One example of deposition is the process by which, in sub-freezing air, water vapor changes directly to ice without first becoming a liquid. This is how snow forms in clouds.

Sublimation:

Sublimation is the transition of a substance directly from the solid to the gas phase, without passing through the intermediate liquid phase.

Vaporization:

Vapourization (or vapourisation) of an element or compound is a phase transition from the liquid phase to vapor.

Condensation:

Condensation is the change of the physical state of matter from gas phase into liquid phase, and is the reverse of vapourisation.

- The changes in the physical states of a substance are reversible in nature.
- These are due to rearrangement of the molecules in a substance, while on other hand; chemical changes are due to change in specific orientation or arrangement of the atoms and groups of the substance.
- Chemical changes may be irreversible or completely or partially reversible.
- Chemical changes always result in a formation of a new compound having different properties.

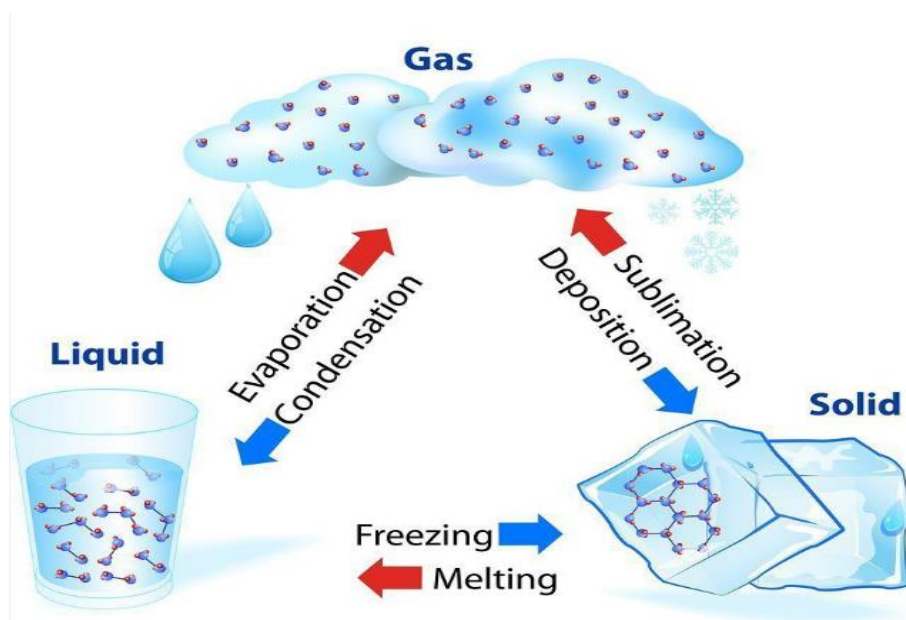


Figure: Changes of states of matter

Latent heat:

- The amount of heat required to raise the temperature of one gram of the solid is called the **heat capacity**.
- The temperature of solid continuously increases until it reaches to its melting point.
- At melting point the temperature will hold steady for a while, even though heat is added to the solid.
- It will hold steady until the solid completely melts. The temperature rising stops because melting requires energy.
- When a change in the state of a material occurs, the temperature usually remains constant but heat is absorbed.
- This heat which results in the change of matter without increasing the temperature is called the **latent heat**.
- When this heat results in the change of state from a solid to liquid it is known as the **latent heat of fusion**.
- For example the heat required to change ice to water at 0°C is the latent heat of fusion.
- Likewise the latent heat of vaporization is the quantity of heat absorbed when a change of state from liquid to vapour occurs at its boiling point without changing the temperature of the material.
- For example the heat required to change water to vapour at 100°C is the **latent heat of vaporization**.
- The molten solid (liquid) has a higher heat capacity than the solid crystalline state therefore it absorbs more heat with a smaller increase in temperature.
- Hence, when a crystalline solid melt it absorbs a certain amount of heat, the latent heat of melting, and it undergoes a change in its heat capacity.

- Any change like melting, freezing, boiling or condensation brought about by heat which has a change in heat capacity and a latent heat involved, is called a **first order transition**.
- Any change brought about by heat, which has a change in heat capacity, but a latent heat is not involved, is called a **second order transition**.
- In first order transition melting is observed with crystalline solid, and in second order transition the glass transition is observed with amorphous solid.

Vapour pressure:

Physical properties of liquids are controlled by **strength and nature of intermolecular attractive forces**. The most important properties are vapour pressure, viscosity, surface tension and light absorption and refraction. A liquid placed in a container partially evaporates to establish a pressure of vapour above the liquid. The established **pressure depends on the nature of the liquid**, and at equilibrium it becomes constant at any given temperature. This constant vapour pressure is the saturated vapour pressure of liquid at that temperature. Until the vapour pressure is maintained, no further evaporation observes.

As shown in Fig, at lower pressures a liquid evaporates into the vapour phase while at higher pressure the vapour tend to condensate till equilibrium establishes. During vaporization heat is absorbed by liquid.

At any given temperature, the amount of heat required per gram of liquid is definite quantity called as **heat of vaporization** of liquid (ΔH_v). It is difference in enthalpies of vapour (H_v) and liquid (H_l), respectively. Therefore,

$$\Delta H_v = H_v - H_l$$

During **evaporation** ΔH_v is always **positive** while during **condensation** it becomes always **negative**. As per definition of change of enthalpy, ΔH_v is the difference in internal energy of vapour and liquid.

$$\Delta H_v = \Delta E_v + P \Delta V_v$$

where,

P is vapour pressure

ΔH_v is change in volume during vapour to liquid transition.

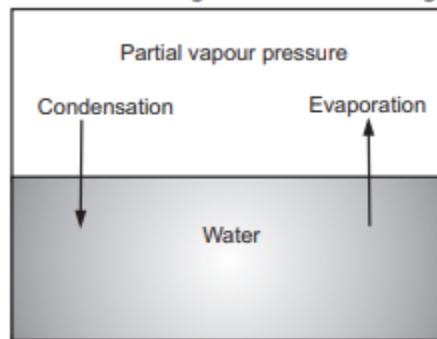


Figure: Schematic Showing Evaporation and Condensation in Liquids with Change in Temperature

The temperature of a substance depends on the average kinetic energy of its molecules. Average kinetic energy is considered because there is an enormous range of kinetic energies for these molecules. Even at temperatures well below the boiling point of a liquid, some of the particles are moving fast enough to escape from the liquid. During this process the average kinetic energy of the liquid decreases. As a result, the liquid becomes cooler. It therefore absorbs energy from its surroundings until it returns to thermal equilibrium. But as soon as this happens, some of the water molecules once again have enough energy to escape from the liquid.

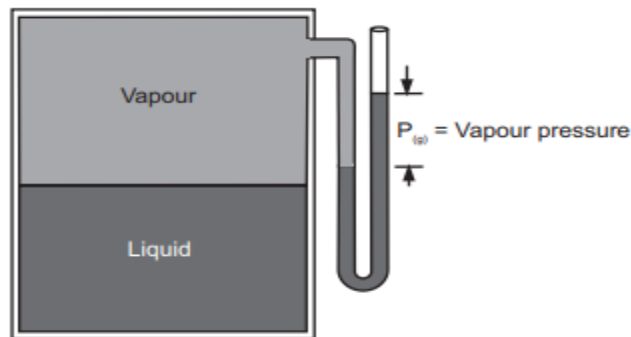


Figure: Closed Container Showing Vapour Pressure of Liquid at Given Temperature

In an open container, this process continues until all the water evaporates. In a closed container, some of the molecules escape from the surface of the liquid to form a vapour. Eventually, **the rate at which the liquid evaporates to form a gas becomes equal to the rate at which the vapour condenses to form the liquid**. At this point, the system is said to be in **equilibrium**.

As shown in Fig, the space above the liquid is saturated with water vapour, and no more water evaporates. The **pressure of the water vapour in a closed container at equilibrium is called the vapour pressure**.

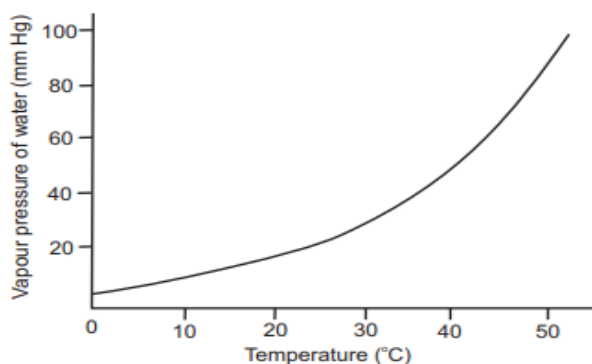


Figure: Plot of Vapour Pressure versus Temperature of Water

The Fig shows that the relationship between vapour pressure and temperature is not linear. The vapour pressure of water increases more rapidly than the temperature of the system.

Measurement of Vapour Pressure:

Vapour pressures of liquids are measured by static and dynamic methods.

Sublimation:

Sublimation is another form of phase transitions. Here solid turns directly into a gas. As a sublimating material **changes from a solid to a gas**, it never passes through the liquid state.

As we know water exists in its three forms namely ice, water, and steam. Sublimation is just one of the ways water or another substance can change between its potential phases. Substances such as **water and carbon dioxide** (CO₂) can be plotted on as pressure vs. temperature to understand their state of matter (solid, liquid, or gas) at a given temperature and pressure.

At a typical atmospheric pressure, water is a solid at temperatures below 0° C, a liquid from 0 to 100° C, and a gas at higher temperatures. But atmospheric pressure, however, can change, particularly with altitude. **Higher altitudes yield lower atmospheric pressures**. Water doesn't always change phase at the same temperatures. For example, with lower pressures, liquid water changes to a gas at temperatures lower than 100° C. If the pressure is dropped low enough, water reaches what's known as a **triple point**. At pressure and temperature of triple point a substance can exist in solid, liquid, and gaseous forms.

Below this point, solid water sublimates, changing directly into a gas with a rise in temperature and never pass through the liquid phase. The CO₂ has a triple point at a pressure higher than 1 atmospheric pressure, meaning that at Earth's standard

atmospheric pressure, CO₂ will sublime as it heats and is converted from solid to a gas.

Critical point:

A liquid need not always have to be heated to its boiling point before it changes to a gas. The kinetic energy of the molecules is proportional to the absolute temperature of the gas. Due to high kinetic energy gas molecules are in the state of constant motion. In liquids, only few molecules have lower or higher kinetic energy. It is illustrated in Fig. At low temperature, the number of molecules having high kinetic energy is less as shown by ABCD while at high temperature the number of molecules having higher kinetic energy increases as shown by FBCE. The molecules with high kinetic energy are important to escape from liquid state to vapour state. Upon cooling, kinetic energy gradually decreases. Since the temperature being decreased a stage is attained at which gas molecules loses their energy that they are unable to overcome forces of attraction between them. This situation brings the gas molecules near to have contact with each other achieving more condensed liquid state. This state also can be possible to achieve by increasing pressure of the gas but it has a limitation that pressure is effective only below specific temperature. This temperature is called as critical temperature. It is defined as the temperature above which gas cannot be liquefied, even if very high pressure is applied.

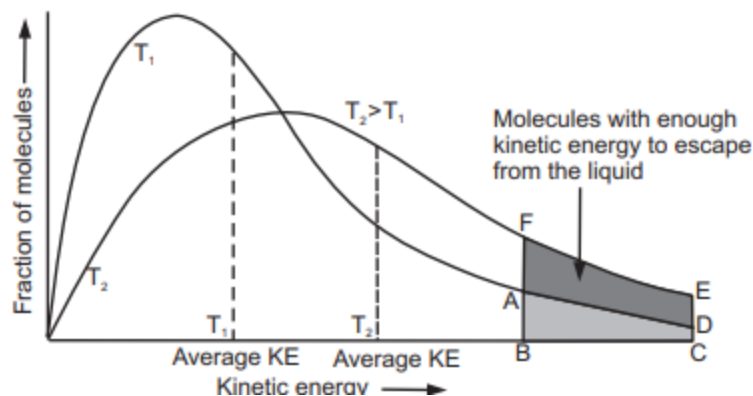


Figure 2.11: Energy Distribution of Molecules in Liquid

The critical temperature of water is $374\text{ }^{\circ}\text{C}$ or 647 K and its critical pressure is 218 atm . If liquid such as water is sealed in evacuated tube, a specific amount of it evaporates to produce vapour at constant temperature. Like gas, water vapour exerts pressure and maintains equilibrium between liquid and vapour phases. Exerted vapour pressure is characteristic of every liquid and is constant at any given temperature.

The vapour pressure of water at $25\text{ }^{\circ}\text{C}$ is 23.76 mmHg while at $10\text{ }^{\circ}\text{C}$ it is 760 mmHg and therefore it is clear that vapour pressure increases continuously with temperature. As water is heated further, it evaporates to more amount resulting in increased vapour pressure.

When temperature reaches $374\text{ }^{\circ}\text{C}$ the water meniscus becomes invisible. At critical temperature, physical properties of liquid and vapour become identical and no distinction can be made between the two. This point is also called as **critical point**. The temperature, saturated vapour pressure and molar volume corresponding to this point are designated as critical temperature (T_c), critical pressure (P_c) and critical volume (V_c) respectively. For water these critical constants are; $T_c = 374\text{ K}$, $P_c = 219.5\text{ atm}$ and $V_c = 58.7\text{ mL/mole}$. The critical points for different gases are given in Table.

Table: Critical Temperatures, Pressures and Boiling Points of Common Gases

Gas	Critical temperature (°C)	Critical pressure (atm)	Boiling point (°C)
He	-267.96	2.261	-268.94
H ₂	-240.17	12.77	-252.76
Ne	-228.71	26.86	-246.1
N ₂	-146.89	33.54	-195.81
CO	-140.23	34.53	-191.49
Ar	-122.44	48.00	-185.87
O ₂	-188.38	50.34	-182.96
CH ₄	-82.60	45.44	-161.49
CO ₂	31.04	72.85	-78.44
NH ₃	132.4	111.3	-33.42
Cl ₂	144.0	78.1	-34.03

The Gibbs Phase Rule:

- Phase rule is an important tool used for the quantitative treatment of systems in equilibrium.
- It enables us to predict the conditions that must be specified for a system to exhibit equilibrium.
- Two or more different phases are present in equilibrium to form heterogeneous system. Such systems are studied by phase rule.
- J. Willard Gibbs enunciated the phase rule in 1876 on the basis of thermodynamic principles. This rule predicts qualitatively the effect of temperature, pressure and concentration on a heterogeneous equilibrium.

Phase rule

The number of degree of freedom (F) of the system is related to number of components (C) and number of phases (P) by the following phase rule equation.

$$F = C - P + 2$$

Explanation or meaning of terms

1. Phase (P)

Any homogeneous physically distinct and mechanically separable portion of a system which is separated from other parts of the system by definite boundaries.

a) Gaseous phase:

All gases are completely miscible and there is no boundary between one gas and the other. For example: air – single phase

b) Liquid phase:

It depends on the number of liquids present and their miscibilities.

- If two liquids are immiscible, they will form three separate phases two liquid phase and one vapour phase. For example: benzene-water.
- If two liquids are miscible, they will form one liquid phase and one vapour phase. For example: alcohol – water.

c) Solid phase:

Every solid constitutes a separate phase

For example:

- (i) Water system ----- three phases
- (ii) Rhombic sulphur (s) -- > monoclinic sulphur (s) ----- two phase
- iii) Sugar solution in water ----- one phase

2. Component (C):

“The smallest number of independently variable constituents, by means of which the composition of each phase can be expressed in the form of a chemical equation”.

For example:

- i) Water system ---- one component (H_2O)
- ii) An aqueous system of NaCl --- two component ($NaCl$, H_2O)

3. Degree of freedom (F)

“The minimum number of independent variable factors such as temperature, pressure and concentration, which must be fixed in order to define the system completely”.

i) Water system:

Ice (s) < --- > water (l) < --- > vapour (g)

F = Non variant (or) zero variant

ii) Ice (s) < --- > water (l)

F = univariant (one)

iii) For a gaseous mixture of N₂ and H₂, we must state both the pressure and temperature.

Hence, the system is bivariant.

Phase diagram:

Phase diagram is a graph obtained by plotting one degree of freedom against another.

Types of phase diagrams:

- P-T Diagram : used for one component system
- T-C Diagram : used for two component system

Applications of phase rule to one component system:

The water system:

Water exists in three possible phases namely solid, liquid and vapour. Hence there can be three forms of equilibria.

Solid < --- > Liquid

Liquid < --- > Vapour

Solid < --- > Vapour

Each of the above equilibrium involves two phases. The phase diagram for the water system is shown in the figure.

This phase diagram contains curves, areas, and triple.

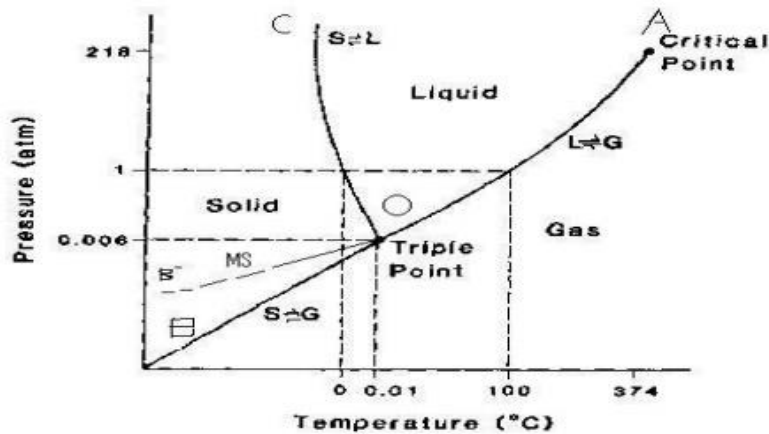


Figure: Phase diagram

(i) Curve OA

The curve OA is called vaporisation curve, it represents the equilibrium between water and vapour. At any point on the curve the following equilibrium will exist.

Water < --- > Water vapour

The degree of freedom of the system is one, i.e, **univariant**.

This is predicted by the phase rule.

$$F=C-P+2; F=1-2+2; F=1$$

This equilibrium (i.e. Line OA) will extend up to the critical temperature (374° C). Beyond the critical temperature the equilibrium will disappear only water vapour will exist.

(ii) Curve OB

The curve OB is called sublimation curve of ice, it represents the equilibrium between ice and vapour. At any point on the curve the following equilibrium will exist.

Ice < --- > Vapour

The degree of freedom of the system is one, i.e. **univariant**. This is predicted by the phase rule.

$$F = C - P + 2; F = 1 - 2 + 2; F = 1$$

This equilibrium (line OB) will extend up to the absolute zero (-273° C), where no vapour can be present and only ice will exist.

iii) **Curve OC**

The curve OC is called melting point curve of ice, it represents the equilibrium between the ice and water. At any point on the curve the following equilibrium will exist.

Ice < --- > water

The curve OC is slightly inclined towards pressure axis. This shows that melting point of ice decreases with increase of pressure.

The degree of freedom of the system is one i.e., **univariant**.

iv) **point O (triple point)**

The three curves OA ,OB ,OC meet at a point “O” ,where three phases namely solid ,liquid and vapour are simultaneously at equilibrium .

This point is called triple point, at this point the following equilibrium will exist.

Ice < --- > water < --- > vapour

The degree of freedom of the system is zero i.e., **nonvariant**.

This is predicted by the phase rule.

$$F = C - P + 2; F = 1 - 3 + 2 = 0$$

Temperature and pressure at the point “O” are 0.0075 °C and 4.58 mm respectively.

(v) **Curve OB': Metastable equilibrium**

The curve OB' is called vapour pressure curve of the super-cool water or metastable equilibrium where the following equilibrium will exist.

Super-cool water < --- > vapour

Sometimes water can be cooled below 0 °C without the formation of ice, this water is called super –cooled water. Super cooled water is unstable and it can be converted in to solid by seeding or by slight disturbance.

vi) **Areas**

Area AOC, BOC, AOB represents water, ice and vapour respectively .The degree of the freedom of the system is two.i.e. **Bivariant**.

This is predicted by the phase rule

$$F=C-P=2; F=1-1+2; F=2$$

Eutectic mixture:

- A eutectic mixture is defined as a mixture of two or more components which usually do not interact to form a new chemical compound but, which at certain ratios, inhibit the crystallization process of one another resulting in a system having a lower melting point than either of the components .
- The temperature at which such system exists in liquid phase is known as eutectic temperature. Above this temperature, the components are liquid and below this temperature they are solids.
- Eutectic mixtures, can be formed between Active Pharmaceutical Ingredients (APIs), between APIs and excipient or between excipient; thereby providing a vast scope for its applications in pharmaceutical industry.
- Physically eutectic systems are solid dispersions. Some examples of this type are thymol – salol, thymol – camphor, menthol – camphor etc.

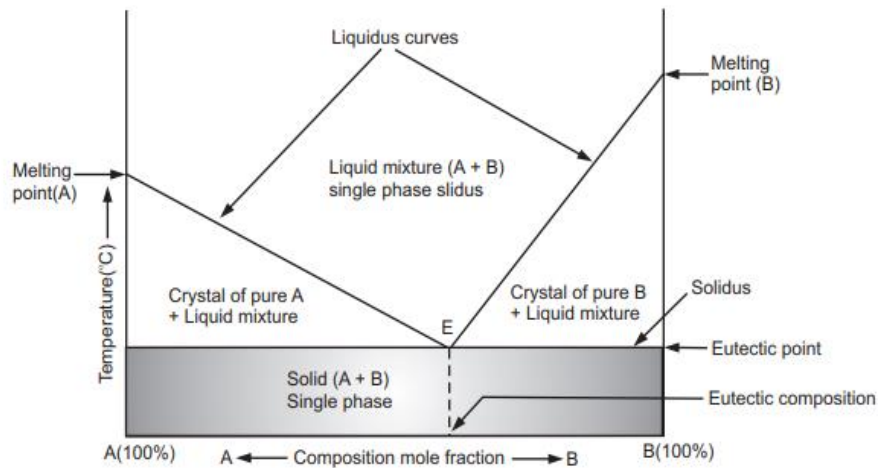


Figure: Eutectic mixture

- In Fig, the melting temperature of two substances A and B are plotted against mixture compositions.
- The curves separating the regions of A + Liquid and B + Liquid from regions of liquid AB are termed liquidus curves.
- The horizontal line separating the fields of A + Liquid and B + Liquid from A + B all solid, is termed the solidus.
- Upon addition of B to A or A to B, their melting points are reduced. The point, E, where the liquidus curves and solidus intersect, is termed the eutectic point.
- At the eutectic point in this two-component system, all three phases, that is Liquid, crystals of A and crystals of B, all exist in equilibrium.
- The eutectic point represents a composition (eutectic mixture composition) at which any mixture of A and B has the lowest melting point. Note that the eutectic is the only point on the diagram where this is true.

- At the eutectic point the maximum numbers of allowable phases are in equilibrium. When this point is reached, the temperature must remain constant until one of the phases disappears.
- A eutectic is an invariant point. Below eutectic temperature no liquid phase exists.
- If we cool solution of A and B which is richer in A than the eutectic mixture, then the crystal of pure A will appear.
- As the solution is cooled further, more and more of A get crystallize out and the solution becomes richer in B.
- When the eutectic point is reached, the remaining solution crystallizes out forming a microcrystalline mixture of pure A and pure B.
- If salol – thymol combinations is to be dispensed as dry powder, it is necessary that the ambient temperature should be below its eutectic point of 13 °C.
- Above this temperature, it exists in liquefied form. At eutectic point their contribution with respect to composition is 34 % thymol and 66 % salol.

Eutectic mixture formation is usually, governed by following factors:

- The components must be miscible in liquid state and mostly immiscible in solid state,
- Intimate contact between eutectic forming materials is necessary for contact induced melting point depression,
- The components should have chemical groups that can interact to form physical bonds such as intermolecular hydrogen bonding etc.,
- The molecules which are in accordance to modified VantHoff's equation can form eutectic mixtures.

Applications of Eutectic Mixtures in Pharmaceutical Industry

- During pre formulation stage, compatibility studies between APIs and excipient play a crucial role in excipient selection.
- Testing for eutectic mixture formation can help in anticipation of probable physical incompatibility between drug and excipient molecules.
- Eutectic mixtures are commonly used in drug designing and delivery processes for various routes of administration. (Table 1) lists few examples of eutectic mixtures and their application.
- During manufacturing of pharmaceutical dosage form, it is extremely necessary to anticipate the formation of eutectics and avoid manufacturing problems if any.
- For example, during tablet compaction the heat produced in the punch and die cavities may lead to fusion or melting of tablet powder compacts leading to manufacturing defects.
- Thus knowledge of eutectic points of powder components may help avoid these problems.
- During pharmaceutical analysis, understanding of eutectic mixtures can help in the identification of compounds having similar melting points.
- Compounds having similar melting points, as a rule will have different eutectic point with a common other component.

Gases:

- The gaseous state is the simplest state amongst the three states of matter.
- The molecules in gas are wide apart in empty space and are free to move in any direction in the container they are contained in.

- The gas molecules exert pressure on the walls of the container in all directions.
- Gases have indefinite expansion ability to fill the entire container.
- If movable piston is fitted into container containing gas, then on application of pressure by piston they get easily compressed.
- When two or more gases placed together they rapidly diffuse throughout each other and form a homogenous mixture.
- Upon heating gas in the container inside pressure increases and if container is fitted with piston under this condition its volume increases.
- Chemical properties of gases vary significantly whereas Physical properties are simpler to understand.
- Gaseous state can be described by considering small scale action of individual molecules or by large action of the gas.
- By studying these properties, we can understand the behaviour of gases. The model called as kinetic molecular theory can easily describe the properties.

Kinetic Molecular Theory of Ideal Gases:

- The statements made in this theory are only for what is called an ideal gas.
- They cannot all be rigorously applied to real gases, but can be used to explain their observed behaviour qualitatively.
- The kinetic molecular theory is based upon the following postulates;
- All matter is composed of tiny discrete particles (molecules or atoms).
- describe the properties.
- Ideal gases consist of small particles (molecules or atoms) that are far apart in comparison to their own size.
- These particles are dimensionless points, which occupy zero volume.

- These particles are in rapid, random and constant straight-line motion. Well-defined and established laws of motion can describe this motion.
- There are no attractive forces between gas molecules or between molecules and the sides of the container with which they collide.
- Molecules collide with one another and the sides of the container.
- Energy can be transferred in collisions among molecules.
- Energy is conserved in these collisions, although one molecule may gain energy at the expense of the other.
- Energy is distributed among the molecules in a fashion known as the Maxwell Boltzmann Distribution.
- At any instant, the molecules in each sample of gas do not at all possess the same amount of energy.
- The average kinetic energy of all the molecules is proportional to the absolute temperature. Above mentioned postulates are meant for ideal gas only and are only approximately valid for real gases.

Characteristics of Gases:

Volume:

- The volume of container is the volume of gas sample and is expressed in unit liter (l) or milliliter (ml).

Pressure:

- Atmospheric pressure is measured using a barometer.
- If a tube, completely filled with mercury (Hg), is inverted into a dish of mercury, mercury will flow out of the tube until the pressure of the column of mercury equals the pressure of the atmosphere on the surface of the mercury in the dish.
- The height of the mercury in the tube is 760 mm for 1 atm of pressure.

- Column of mercury is used to measure pressure of a gas closed in a container.
- The height 'h' of mercury column of manometer indicate how much higher the pressure of gas is in the container than outside.
- Pressure of a gas is proportional to average force per unit area that gas molecules exert on the walls of the container.
- The greater the number of gas molecules in each container, the higher is the pressure as the greater average number of collisions occurring with the wall of the container.
- If the volume of the container is reduced, the average number of collisions will increase.
- Pressure is directly proportional to the kinetic energy of the gas molecules therefore higher the temperature the greater is the kinetic energy and greater the pressure of the gas.

Temperature:

- Temperature of gas is measured in Kelvin temperature scale.
- The product of pressure and volume per mole is proportional to the average molecular kinetic energy.
- The average kinetic energy is proportional to the absolute temperature.

Gas laws:

Ideal gas law

- The ideal gas law illustrates the relationship between pressure, volume , temperature and moles.
- The formula for the ideal gas law is $PV = nRT$

Where,

P = Pressure

V = Volume

n = Moles

T = Temperature

R = The Ideal Gas Constant

Boyle's Law

- Boyle's law gives the relationship between the pressure of a gas and the volume of the gas at a constant temperature.
- Basically, the volume of a gas is inversely proportional to the pressure of a gas at a constant temperature.

$$V \propto 1/P \text{ or}$$

$$P \propto 1/V \text{ or}$$

$$PV = k_1$$

- Where V is the volume of the gas, P is the pressure of the gas and K_1 is the constant.
- It can be used to determine the current pressure or volume of gas and can be represented also as;

$$P_1V_1=P_2V_2$$

Charle's law

- Charle's law states that at constant pressure, the volume of a gas is directly proportional to the temperature (in Kelvin) in a closed system.
- Basically, this law describes the relationship between the temperature and volume of the gas.
- Mathematically, Charle's law can be expressed as;

$$V \propto T$$

- Where, V = volume of gas,
T = temperature of the gas in Kelvin.
- Another form of this equation can be written as;

$$V_1 / T_1 = V_2 / T_2$$

Gay-Lussac Law

- Gay-Lussac law gives the relationship between temperature and pressure at constant volume.
- The law states that at a constant volume, the pressure of the gas is directly proportional to the temperature for a given gas.
- If you heat up a gas, the molecules will be given more energy, they move faster.
- If you cool down the molecules, they slow down and the pressure decreases.
- The change in temperature and pressure can be calculated using Gay-Lussac law and it is mathematically represented as;

$$P \propto T \text{ or}$$

$$P / T = k_1 \text{ or}$$

$$P_1 / T_1 = P_2 / T_2$$

- Where P is the pressure of the gas and T is the temperature of the gas in Kelvin.

Avogadro's Law

- Avogadro's law states that if the gas is an ideal gas, the same number of molecules exists in the system.
- The law also states that if the volume of gases is equal it means that the number of the molecule will be the same as the ideal gas only when it has equal volume.
- The above statement can be mathematically expressed as;

$$V / n = \text{constant or}$$

$$V_1 / n_1 = V_2 / n_2$$

- Where V is the volume of an ideal gas and n in the above equation represent the number of gas molecules.

Aerosol:

- Liquefaction of a gas can be achieved by applying pressure on it and keep the temperature below the critical temperature.
- When the pressure is reduced, the molecules expand and the liquid reverts back to the gaseous state.
- Aerosols are based on the principle of reversible change of state on the application and release of pressure.
- In pharmaceutical aerosols, a drug is dissolved or suspended in a propellant, a material which exists as a liquid under the pressure conditions prevalent inside the container but gets converted to a gas under normal atmospheric conditions.

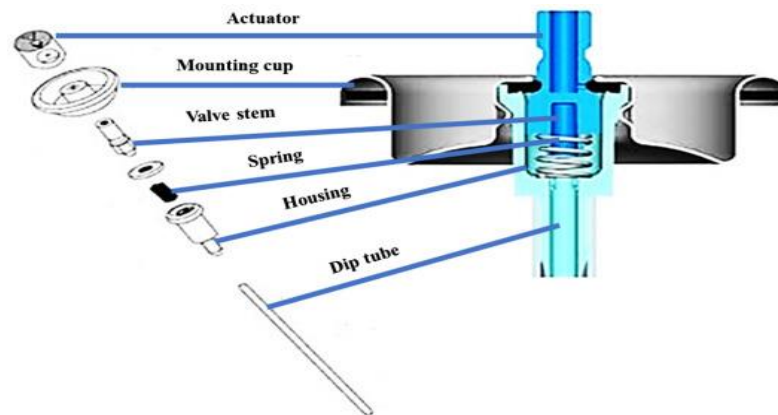


Figure: Components of aerosol

- The container is designed in such a manner that on depressing a valve, some of the drug-propellant mixture is expelled out due to the excess pressure inside the container.

- The propellant used in such a products are generally fluorinated hydrocarbons although gases such as nitrogen and carbon dioxide and also being used.
- The aerosol containers are filled either by cooling the propellant and drug to a low temperature within the container which is then sealed with the valve.
- Alternatively, the drug is sealed in the container at room temperature and the required quantity of propellant is forced into the container under pressure.
- In both the cases, when the container is at room temperature, part of the propellant is in the gaseous state and exerts pressure necessary to extrude the drug while the remaining is in the liquid state and provides a solution or suspension vehicle for the drug.
- Generally, pharmaceutical aerosols are stored in two types of inhalers viz.,
 - Metered-Dose Inhalers (MDIs)
 - Dry Powder Inhalers (DPIs).
- MDIs and DPIs deliver a specific quantity of drug to the lungs through pulmonary tracks on external surface of body parts.
- Both types of products are used to treat lung diseases characterized by obstruction of airflow and shortness of breath, including asthma and chronic obstructive pulmonary disease (COPD), as well as respiratory infections and cystic fibrosis.
- The inhalation route offers further potential for systemic drug delivery.

MDI:

- The MDI is used to provide a certain dose of an aerosol of medication. It is likely to be either: Salbutamol, Salmeterol, or one that includes a small dose of steroid such as Fluticasone, Seretide, Fostair.

- These work by relaxing the muscles of the large airways and/or reducing the inflammation of the airways.

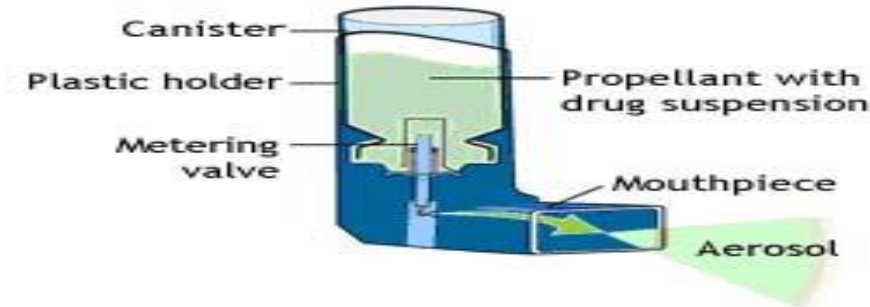


Figure: Metered dose inhaler

Dry powder inhalers:

- Dry powder inhalers are an alternative to the aerosol based inhalers commonly MDIs, that deliver a powder dosage form to the lungs.
- Most DPIs include an active ingredient and one or more excipients to aid powder dispersion and flow.
- The powder dose from a DPI can be analyzed on the PSA300 image analysis system.
- The optimum aerodynamic particle size distribution for most inhalation aerosols is very important and these are generally in the range of 1-5 μm .
- Depending on the nature of the product concentrate, the aerosol can be filled by a cold filling or a pressure filling process.'
- The aerosol products can be filled in two ways:
 - ✓ Cold-fill process.
 - ✓ Pressure-fill process.

Packaging of aerosols:

Cold-fill process:

- This process is used to fill metered aerosol products using a fluorocarbon propellant.
- By lowering the temperature of a propellant below its boiling point, the propellant becomes liquid at atmospheric pressure.
- The active ingredients or concentrate and propellant are cooled to a low temperature of about -300 to -40 °F.
- The chilled concentrate is poured into the chilled container and propellant is added.
- Sufficient time is given for the propellant to partially vaporise, in order to expel the air present in the container.
- The valve is fitted on to the container which is placed into a water bath so that the contents are heated to 130°F (54°C) in order to check any leakage and strength of container.
- A dry ice-acetone bath is used to obtain the desired low temperature for laboratory scale preparation whereas refrigeration equipment is used for the large scale production of aerosols.

Pressure-fill process:

- This process is used for filling aerosols containing hydrocarbon propellant.
- The product concentrate is placed into the container and the valve is sealed.
- The propellant is forced through the valve under pressure.
- After this the container is immersed in a water bath at 130 °F (or 54 °C) in order to check any leakage and strength of the container.
- It is essential that the air present in the container must be expelled before filling the contents into the aerosol container.

Applications:

- Administration of drugs from an aerosol is very easy and they can be applied directly on the affected parts or abraded skin introduced into body cavity and passages.
- When sprayed on skin, some of propellants (e.g., ethyl chloride) cool the tissue due to sudden expansion of propellant.
- For these reasons, pharmaceutical aerosols have a wide range of applications in the treatment of a patient due to its beneficial effect over the other dosage form.
- It is used very effective treatment of illness of asthma and chronic obstructive pulmonary disease (COPD).

Relative humidity:

- The percentage of water vapor that is actually in the air compared to the amount of water vapor the air can hold.

$$\text{Relative humidity} = \frac{\text{Actual water vapour pressure}}{\text{Saturated water vapour pressure}} \times 100$$

- Relative humidity is the amount of water vapor (vapor pressure) that is in the air.
- It is a percentage of how much moisture the air could possibly hold.
- The amount of vapor that can be contained in the air increases with temperature.
- Relative humidity is a combination function of the actual moisture content of the air, the temperature, and the barometric pressure.
- The higher the percentage of relative humidity, the more humid (moist) the air feels, while a lower percentage usually feels drier.

- Saturation occurs when air is holding the maximum amount of water vapor possible at the existing pressure and temperature.
- Saturation is equal to 100% relative humidity, resulting in precipitation.

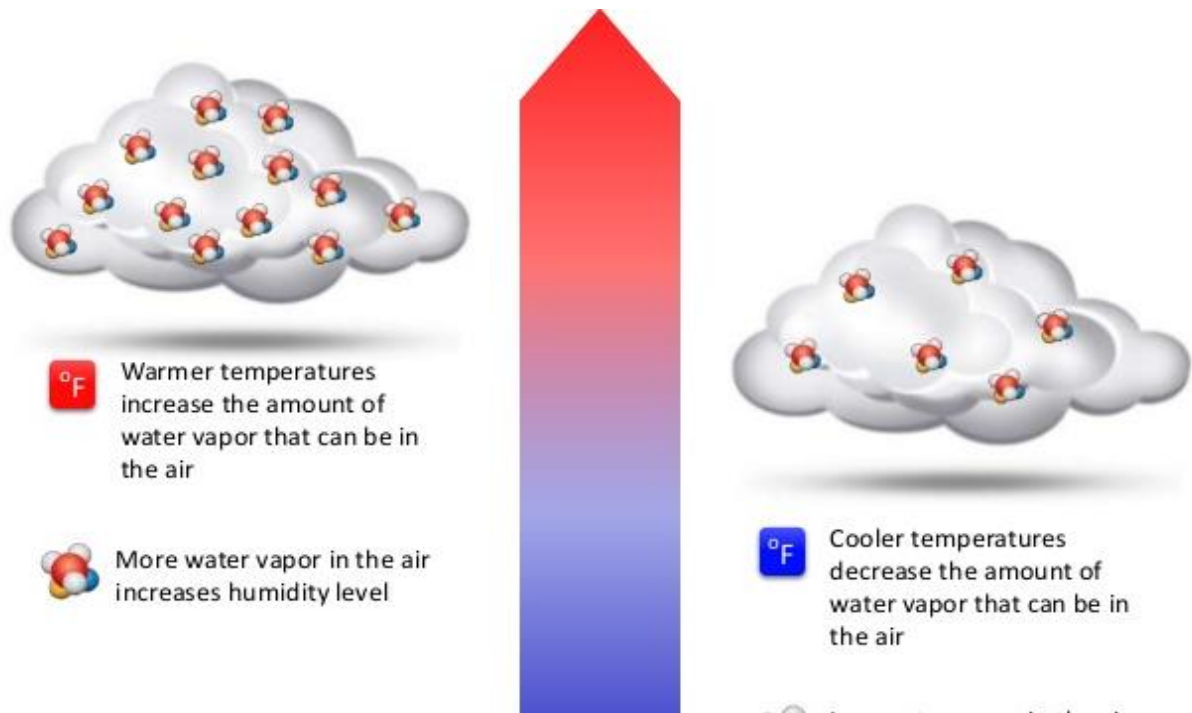


Figure: Relative humidity

Effects of High Humidity

- High humidity causes products to absorb the excess moisture in the air, which can be just as destructive as environments with low humidity.
- Too much humidity can compromise potency and effectiveness, leading to degradation or even toxicity in some products.
- The potential for danger comes when relative humidity levels reach 60 percent or more; giving viruses, bacteria, mold, fungi and mites the opportunity to grow.

Effects of Low Humidity

- Static buildup is a major effect of relative humidity levels dropping below 45 percent.
- The accumulation of static charges can dry out medications, affecting the intended behavior of any solvents used in production.
- The excess static can also cause products to dry out and crumble, or stick together, leading to problems during tablet pressing and packaging.
- An overabundance of moisture can also affect production.
- When products absorb extra moisture, it causes them to either crumble or become sticky, which could clog machinery and bring production to a sudden halt.

Liquefaction of gases:

Liquid complexes:

- Complex fluids are binary mixtures that have a coexistence between two phases: solid–liquid (suspensions or solutions of macromolecules such as polymers), solid–gas (granular), liquid–gas (foams) or liquid–liquid (emulsions).
- They exhibit unusual mechanical responses to applied stress or strain due to the geometrical constraints that the phase coexistence imposes.
- The mechanical response includes transitions between solid-like and fluid-like behavior as well as fluctuations.
- Their mechanical properties can be attributed to characteristics such as high disorder, caging, and clustering on multiple length scales.
- Not every liquid becomes complex on cooling.

- Three-dimensional (3D) liquids with simple two-particle interactions (molten metal's and salts, liquefied noble gases, Morse particles) aggressively crystallize on cooling before they show any significant signs of complexity.
- Classical 3D complex liquids have complicated and competing interactions and special supercooling regimes are necessary to avoid crystallization on supercooling.
- Two-dimensional (2D) liquids with simple interactions have a continuous or almost continuous crossover from simple liquid state to crystal.
- At crossover temperatures, particles in these equilibrium liquids aggregate to form a dynamic mosaic of crystalline-ordered regions (crystallites) and less-ordered clusters.
- At the high-temperature end of the mosaic states, crystallites are small and separated island of order in a disordered (amorphous) matrix.
- Crystallites fraction of the system increases at lower temperatures where crystallinity percolates.
- At even lower temperatures, crystallites merge into a multiconnected crystalline matrix with expected algebraic decay of orientation order (hexatic liquid) or long range order.
- The mosaic is a feature observed at temperatures where the correlation length for orientations is finite and the 2D liquid is in normal (not hexatic) state.
- Shaving cream is an example of a complex fluid. Without stress, the foam appears to be a solid: it does not flow and can support (very) light loads.
- However, when adequate stress is applied, shaving cream flows easily like a fluid.

- On the level of individual bubbles, the flow is due to rearrangements of small collections of bubbles.
- On this scale, the flow is not smooth, but instead consists of fluctuations due to rearrangements of the bubbles and releases of stress.

Liquid Crystals

- In addition to the three States of matter, some asymmetric molecules often exhibit a fourth state known as a liquid crystalline state or mesophase.
- Liquid crystals possess some of the properties of liquid and some of solids.
- For example liquid crystal possesses the property of mobility and rotation and thus can be considered to have the flow properties of liquid.
- On the other hand, these also possess the properties of birefringence, a property of associated with solid crystals.
- The birefringence, the light passing through a material is divided into two components with different velocities and hence different refractive index.

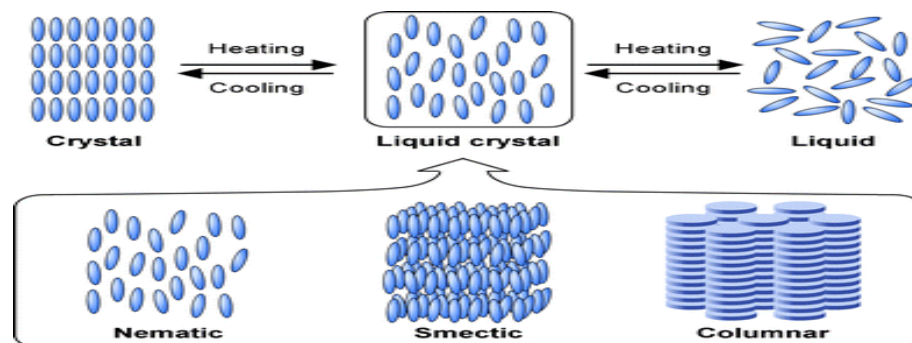


Figure: Types of liquid crystals

- The two main types of structure of liquid crystal are the smectic (soap or grease like) and nematic (thread like).

- In the smectic state, the molecules are mobile in two directions and show rotation about one axis.
- In the nematic state, the molecules are mobile in three dimensions.
- A third type known as the cholesteric crystals exist but may be considered as a special case of the nematic type.
- The liquid crystalline state is found widespread in nature—in nerve, brain tissue and blood vessels.
- Atherosclerosis is thought to result from the deposition of liquid in the liquid crystalline state on the wall of blood vessels.
- The three components of bile, the cholesterol, the bile salt and water when present in a definite proportion can result in the formation of smectic crystals and these may be involved in the formation of gall stones.
- Certain smectic crystals are believed to be involved in the stabilization of emulsion and have been used for the solubilization of water in soluble materials.

Glassy state:

- The glassy state of materials refers to a nonequilibrium, solid state, such as is typical of inorganic glasses, synthetic noncrystalline polymers and food components.
- Characteristics of the glassy state include transparency, solid appearance and brittleness.
- In such systems, molecules have no ordered structure and the volume of the system is larger than that of crystalline systems with the same composition.
- These systems are often referred to as amorphous (i.e., disordered) solids (e.g., glass) or super cooled liquids (e.g., rubber, leather, syrup).

- Glasses are generally formed by melting crystalline materials at very high temperatures.
- When the melt cools, the atoms are enclosed in a random (disordered) state before they can form in a perfect crystalline arrangement.

Types: There are three types of glassy states-

The first type:

- It is characterized by the cessation of the vibratory movement of rotation of the molecules in a defined (critical) temperature region.
- This results in stabilization of the chain structures of rigidly associated polar molecules (by means of dipoles).

The second type:

- It consists of organic glassy polymerization products.
- These glasses in the stabilized state have fibrous structure of rigid valence bonded carbon atoms with small lateral branches in the form of hydrogen atoms or more complex radicals.

The Third type:

- The third most extensive type of glassy state consists of refractory inorganic compounds of multivalent elements.
- These glasses in the stabilized state have the most thermostable chemical structure in the form of a three-dimensional rigid atomic valency-bonded spatial network.

Solids:

- The state, in which a substance has no tendency to flow under stress, resists forces that tend to deform it, and remain in definite size and shape is called as solid state.

- In solid state the molecules are closely bound to one another.
- A solid hold its shape. The volume of solid is fixed by the shape of solid.
- There are two types of solids namely; crystalline solids and amorphous solids.
- They differ from one another by the way their particles are arranged and their melting points.

Crystalline Solids:

- Atoms, molecules or ions are the units that constitute crystalline system.
- The structural units of crystalline solids such as ice, menthol or sodium chloride are arranged in a fixed geometric pattern or lattices.
- Crystalline solids have definite shape and its units have an orderly arrangement as well as they are practically incompressible.
- Crystalline solid have definite melting points and so they pass sharply from solid to liquid state.
- The binding force between the crystals is electrostatic attraction of the oppositely charged ions.
- In case of organic compounds hydrogen bonding and van der Waals forces are responsible for holding the molecules in crystals whereas in graphite and diamond, the carbon molecules are covalently bond together.
- Depending upon the nature of units which occupy the lattice points, crystals are classified as follows.

Types of Crystals:

Molecular Crystal:

- Molecular crystal consists of specific molecules, which do not carry charge.

- Dipole-dipole and van der Waal's forces hold the molecules of molecular crystal.
- It has less binding energy due to low heat of vaporization which is energy required to separate the molecules from one another.
- Also it has low heat of fusion, which is heat required to increase the interatomic and intermolecular distances in crystals.
- The increase in distances between atoms and molecules allows melting to occur.
- These types of crystals are bound by weak forces and therefore, generally have low melting and boiling points and are volatile in nature.
- They are soft and easily compressible as well as can easily distort.
- As no charge is present in them they are bad conductors of electricity in solid as well as in the liquid state.

Covalent Crystal:

- The lattice of covalent crystal consists of atoms joined together by covalent bonds.
- The examples of these crystals are diamond, graphite, silicone and most organic crystals.
- The bond strength and mutual orientation are the most typical atomic features of covalent materials.
- Iodine is also a covalent crystal because it has 10 times higher lattice energy.

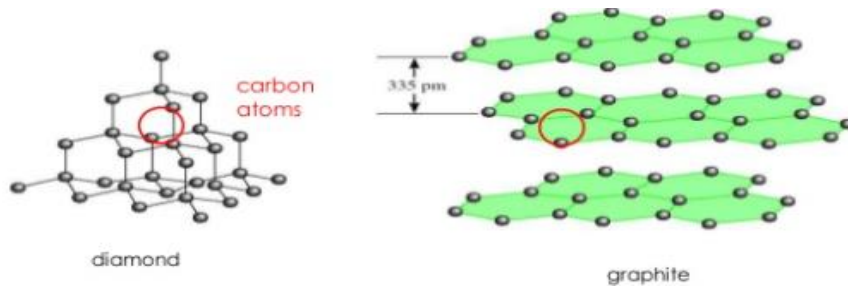


Figure: Covalent crystal

Metallic Crystal:

- Metallic crystals consist of positively charged ion in the field of free flowing electrons.
- The force that binds metal ions (kelmel) to a number of electrons within its sphere of influence is nothing but the net metallic bond.
- The force of attraction between metallic crystals is very strong and therefore they are compact and solid in nature.
- Major characteristics of these crystals are that they are good conductors of heat and electricity, hard and tough, malleable and ductile, exhibit luster when freshly cut, have high melting and boiling points with exception of alkali metals, possess elasticity and have high tensile strength.

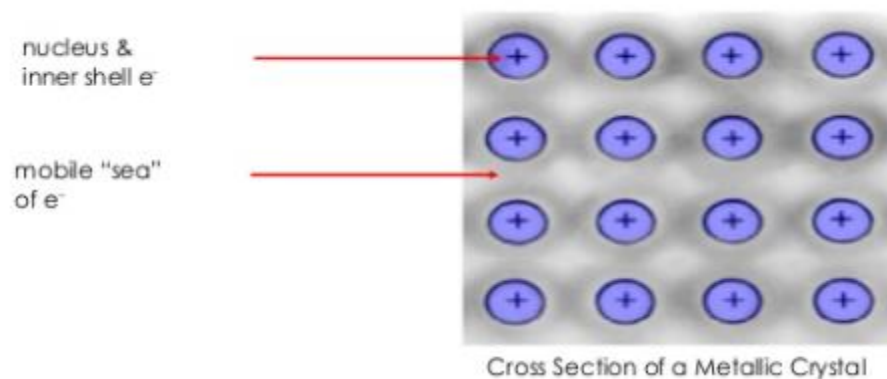


Figure: Metallic crystal

Ionic Crystal:

- The unit of ionic crystals consists of positive and negative ions, for example, $\text{Na}^+ \text{Cl}^-$.

- Coulombic forces of attraction between all ions of opposite charge hold the Na^+ and Cl^- ions.
- These forces are strong and therefore require high-energy input to separate them from one another.
- They have high heats of vaporization, low vapour pressure, high melting and boiling points and are hard and brittle.
- They are insulators in solid state and good conductors of electricity when dissolved in water.
- They dissolve in all polar solvents.

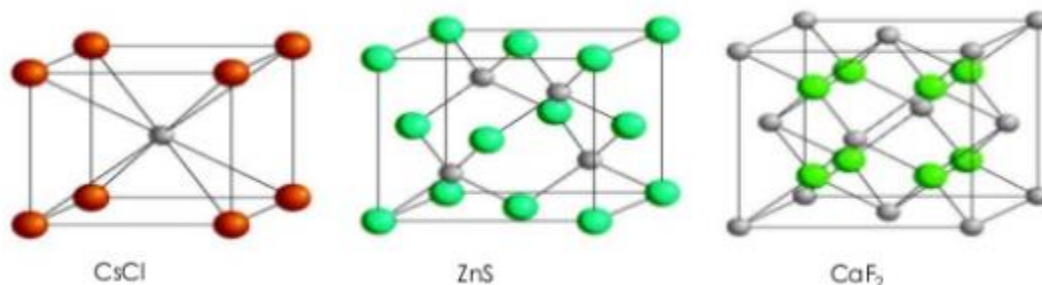


Figure: Ionic crystal

Amorphous solids:

- A state of substance that consists of disordered arrangement of molecules or that do not possess distinguishable crystal lattice is called as amorphous state.
- Amorphous substances do not have characteristic melting points but they soften over wide temperature range, generally, lower than melting point of crystalline forms of same compounds.
- The common examples of amorphous solids are glass and plastics.
- Amorphous character is also common with polymeric molecules used as excipient and large peptides and proteins used as therapeutics agents.
- In addition, it also occurs with small organic and inorganic molecules.

- For most substances, the amorphous form is unstable, returning to more stable crystalline form in a few minutes or hours.
- In pharmaceutical viewpoint, the beauty of amorphous forms is that they have a higher dissolution rates and solubilities than the crystalline forms.
- The reason behind this is the energy required for molecule of a drug to escape from a crystal form is much greater than required for amorphous form.
- However, very few drugs are naturally amorphous.
- The examples of amorphous drugs are accupril/accuretic used to treat high blood pressure and intraconazole used as an acne medication.
- When drug should not dissolve in water it should not be then in amorphous form.
- Solubility and oral bioavailability of a poorly water soluble drug can be improved by different techniques so that it can exist in an amorphous state in the product even after storing at a stressed condition.
- There are four main ways by which amorphous character is induced in a solid.
- These are condensation from vapour state, supercooling of melt, mechanical activation of crystalline mass (during milling) and rapid precipitation from solution during freeze-drying or spray drying.
- Solid dispersions of drug in polymers are widely used to obtain the amorphous state of materials.
- However amorphous state is unstable and may create possibility that during processing or storage the amorphous state may spontaneously convert back to the crystalline state.

- An estimation method for the physical stability of amorphous drug and a clarification of the effect of polymer on crystallization of amorphous drug in solid dispersion are primarily required.
- The difference between amorphous and crystalline solids is important in synthetic procedure of drug design.

S.No	Crystalline Solids	Amorphous Solids
1.	Crystalline solids are arranged in neat and orderly fashion as fixed 3D crystal lattice or geometric patterns. Examples are ice, methanol, penicillin G and sodium chloride.	Amorphous solids are just strewn in any old fashion with random unoriented molecules. Examples are glass, plastic, penicillin G, and novobiocin.
2.	Practically incompressible.	Practically compressible.
3.	Crystalline solids show definite melting point so they pass sharply from solid to liquid state.	Amorphous solids do not show definite melting point so transition from solid to liquid takes place at wide temperature range.
4.	Higher energy is required for molecule to escape from a crystal form.	Low energy is required for molecule to escape from an amorphous form.
5.	Take less time to remove solvent through the space between crystals.	Take comparatively more time to remove solvent and is removed by diffusion.
6.	Handling quality of crystalline materials is poor.	Handling quality of amorphous materials is better.
7.	Shows poor aqueous solubility because more energy required by orderly arranged molecules for	Shows good aqueous solubility because minimal energy required by randomly arranged molecules for

	dissolution.	dissolution.
8.	In crystalline solids melting happens.	In amorphous form glass transition happens.
9.	When crystalline solid is heated at a constant rate, the temperature increases at a constant rate.	When crystalline solid is heated at a constant rate, the temperature increases at different rates.
10.	They show poor absorption and low bioavailability.	They are rapidly absorbed and show higher bioavailability.
11.	These solids are stable than amorphous solids.	They are less stable than crystalline solids.

Polymorphism:

- Pharmaceutical solids rarely exist as 100% crystalline or 100% amorphous forms.
- Many substances due to differences in their intermolecular forces exist in more than one crystalline or amorphous form.
- These forms are called as polymorphs and substances are called polymorphic. Polymorphism is the ability of a molecule to crystallize into more than one different crystal structure.
- The term allotropy used for elements is synonymous to the polymorphism.
- That means, polymorphs have same molecular composition but have different crystalline forms.
- Substance in two different forms is called dimorphic while in three forms called trimorphic and so on.

- Polymorphs are chemically same but are different with respect to physicochemical properties.
- The different forms have different thermodynamic properties such as lattice energy, melting point, and x-ray diffraction pattern; vapour pressure, intrinsic solubility, and the biological activity.
- The difference between polymorphs is variation in packing, shape of crystal and conformation of the molecules.
- Different crystallization processes by different solvents, different rate of cooling and different pressures obtain different polymorphs during crystallization.
- Almost all long-chain organic compounds exhibit polymorphism.
- Many drugs such as steroids (cortisone, testosterone, and prednesolone), barbiturates and sulphonamides show property of polymorphism.
- Sulphanilamide exist in four different α , β , γ and δ polymorphic forms.
- First three polymorphs are of monoclinic crystal type while fourth one is different than previous ones.
- Mebendazole has three polymorphic forms namely; Form A, B and C.
- Anthelmintic activity of one form is more than other.
- Other examples of drugs that show polymorphism are oxytetracycline, mefenamic acid, phenyl butazone, terfenadine etc. Genetic variation i.e. variation in DNA is also a kind of polymorphism.
- Types of Polymorphs: The two polymorphs cannot be converted into one another without undergoing a phase transition.

Monotropic: When polymorphic change is not reversible the system is called monotropic.

- It occurs when one form is stable while other is metastable.
- Metastable form may be converted to stable form over the time.

- The vapour pressure of both forms are different therefore no transition temperature exists. Example: phosphorus.
- The transition point is above the melting points of both polymorphs.

Enantiotropic:

- If the change from one polymorph to another is reversible, the system is called enantiotropic.
- At definite temperature one form is converted to other form. Both forms have different vapour pressures.
- For example rhombic α form of sulphur is converted to other monoclinic β form upon heating at 95.6 °C and cooling at same temperature again it exist in its original form and therefore they are enantiotropic.

Pseudopolymorphs:

- Pseudopolymorphs, i.e., co-crystals are also studied along with polymorphism, which are solid crystalline materials comprising two or more molecules or atoms in the same crystal lattice.
- Co-crystals are also generally characterized as hydrates (solvent trapped), solvates (solvent present), and clathrates (molecules trapped).
- The first co-crystals reported were the co-crystals of hydroquinone and quinone in 1844 by Friedrich Wöhle.
- Co-crystals directly affect the solid-state properties in terms of solubility and bioavailability.
- Co-crystals are frequently designed for pharmaceutical formulations and many pharmaceutical products like tropomyosin and troponin, have been already designed by virtue of the co-crystal phenomenon.
- The most stable polymorph should be employed in the marketed formulation to prevent polymorphic alterations during manufacturing, delivery, or storage.

- In general, the selected polymorph should be thermodynamically stable during the drug development process and remain stable during the manufacturing process too.

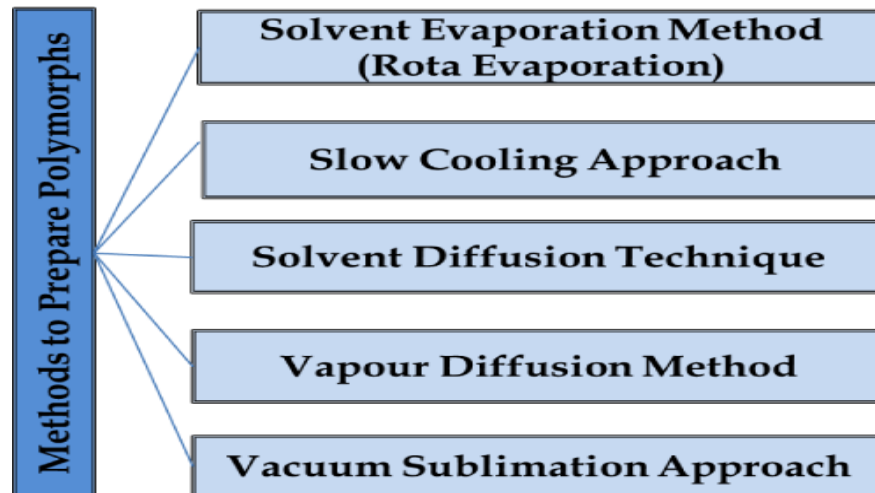


Figure: Methods of preparation of polymorphs

Importance of Polymorphism:

- Polymorphism is pharmaceutically most important because different polymorphs exhibit different physicochemical properties.
- It affects mechanical strength and other formulation aspects like compressibility, flowability, hardness and binding strength etc.
- Unstable polymorphs are not suitable in design of dosage forms because they get converted to stable polymorphs.
- Metastable polymorphs have higher energy level than the stable form.
- Metastable forms exhibit greater dissolution rates, better bioavailability and superior therapeutic activity.

As far as dosage form development is concerned, following general rules are advised for the APIs which show polymorphism:

(a) Selection of the lowest energy polymorph as it is the most thermodynamically stable form;

(b) Avoidance of the metastable forms, though they are more physically stable, but chemically less stable. Attempts should be made to play with the excipients to achieve the set pharmaceutical goals, instead of selecting the metastable form;

(c) Maintenance of such conditions which will avoid transitions from metastable form to the stable form throughout the shelf-life of the product, if the former form is selected due to a particular reason like bioavailability enhancement;

(d) Assurance of avoidance of any polymorphic transition in the dosage form throughout its shelf-life, if so, the same should not significantly affect the product quality and bioavailability