

FACULTY OF PHARMACEUTICAL SCIENCES

- PDM UNIVERSITY -

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Bahadurgarh, Delhi NCR

B.Pharma 3rd Sem

BP302T **Physical Pharmacy (Theory)**

Unit II (A): States of Matter and properties of Matter

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.

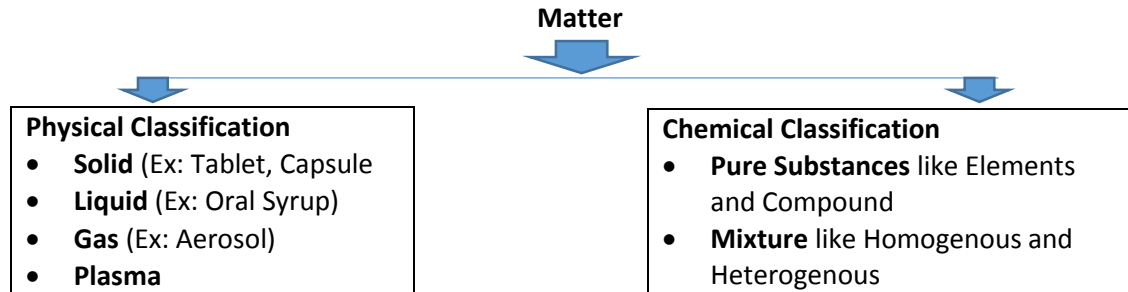
Physicochemical properties of drug molecules: Refractive index, optical rotation, dielectric constant, dipole moment, dissociation constant, determinations and applications

Outline of the Chapter:

Topics	Deals with
1. State of matter	<i>Matter and types</i>
2. Changes in the state of matter 3. Latent heats 4. Vapour pressure 5. Sublimation critical point 6. Eutectic mixtures	<i>Changes of Phases</i>
7. Gases 8. Aerosols – Inhalers 9. Relative Humidity	<i>Gas</i>
10. Liquid complexes 11. Liquid crystals 12. Glassy states	<i>Liquid</i>
13. Solid Crystalline 14. Amorphous 15. Polymorphism.	<i>Solid</i>

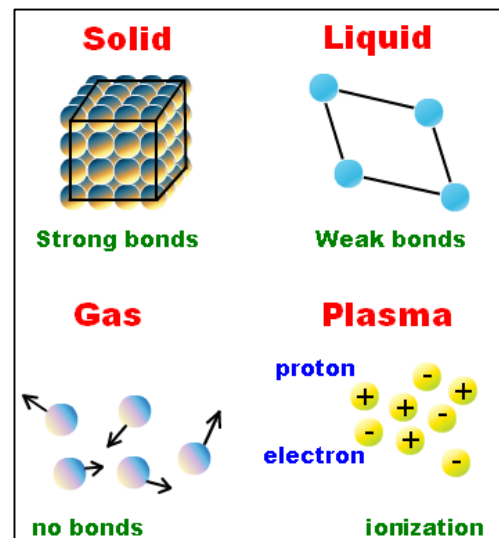
1. State of matter:

Matter is a substance which occupies space and possesses rest mass, especially as distinct from energy. Matters can be classify various ways like Physical Classification, Chemical Classification and General Classification.



Gases, liquids, and crystalline solids are the three primary states of matter or phases. The molecules, atoms, and ions in the solid state are held in close proximity by intermolecular, interatomic, or ionic forces. The atoms in the solid can oscillate only about fixed positions. As the temperature of a solid substance is raised, the atoms acquire sufficient energy to disrupt the ordered arrangement of the lattice and pass into the liquid form. Finally, when sufficient energy is supplied, the atoms or molecules pass into the gaseous state. Solids with high vapor pressures, such as iodine and camphor, can pass directly from the solid to the gaseous state without melting at room temperature. This process is known as *sublimation*, and the reverse process, that is, condensation to the solid state, may be referred to as *deposition*.

Certain molecules frequently exhibit a fourth phase, more properly termed a *mesophase* (Greek *mesos*, middle), which lies between the liquid and crystalline states. This so-called *liquid crystalline* state is discussed later. Supercritical fluids are also considered a mesophase, in this case a state of matter that exists under high pressure and temperature and has properties that are intermediate between those of liquids and gases. Supercritical fluids will also be discussed later because of their increased utilization in pharmaceutical agent processing.



But according to modern days Scientists there are 12 States of Matter:

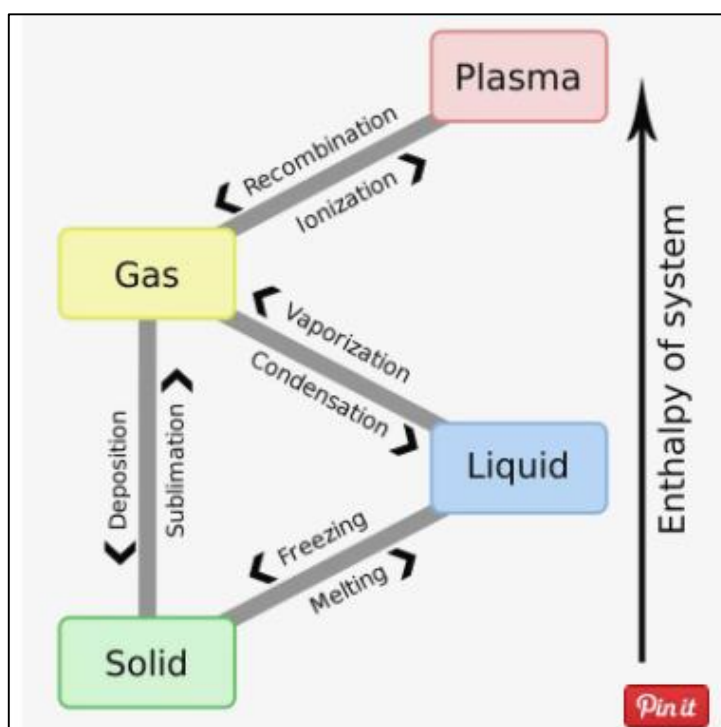
- | | |
|----------------|-----------------------------|
| 1. Solid | 7. Bose-Einstein condensate |
| 2. Liquid | 8. Fermionic condensate |
| 3. Gas | 9. String-net liquid |
| 4. Plasma | 10. Super-critical fluid |
| 5. Super fluid | 11. Colloid |
| 6. Super solid | 12. Degenerate matter. |

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2. changes in the state of matter,



- **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, as well as how frost and hoar frost form on the ground or other surfaces.
- **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.

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3. Latent heats:

In **Latent heat**, energy absorbed or released by a substance during a change in its physical state (phase) that occurs **without changing its temperature**.

The latent heat associated with melting a solid or freezing a liquid is called the heat of fusion; that associated with vaporizing a liquid or a solid or condensing a vapour is called the heat of vaporization.

The latent heat is normally expressed as the amount of heat (in units of joules or calories) per mole or unit mass of the substance undergoing a change of state.

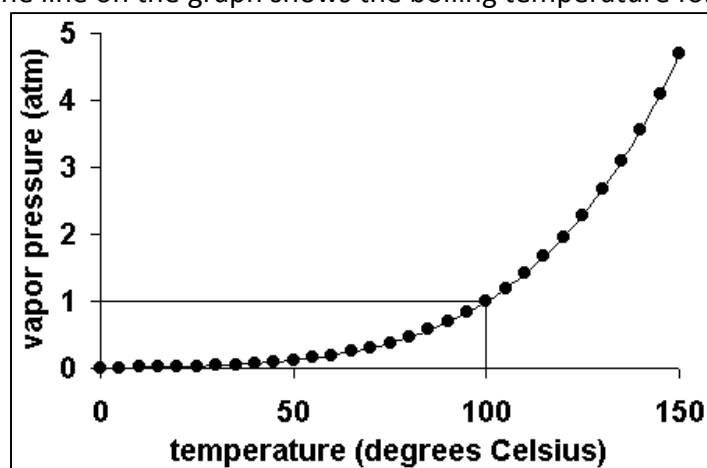
Examples are latent heat of fusion and latent heat of vaporization involved in phase changes, i.e. a substance condensing or vaporizing at a specified temperature and pressure.

4. Vapour pressure:

The vapor pressure of a liquid is the equilibrium pressure of a vapor above its liquid (or solid); that is, the pressure of the vapor resulting from evaporation of a liquid (or solid) above a sample of the liquid (or solid) in a closed container. Examples:

substance	vapor pressure at 25°C
diethyl ether	0.7 atm
bromine	0.3 atm
ethyl alcohol	0.08 atm
water	0.03 atm

The vapor pressure of a liquid varies with its temperature, as the following graph shows for water. The line on the graph shows the boiling temperature for water.



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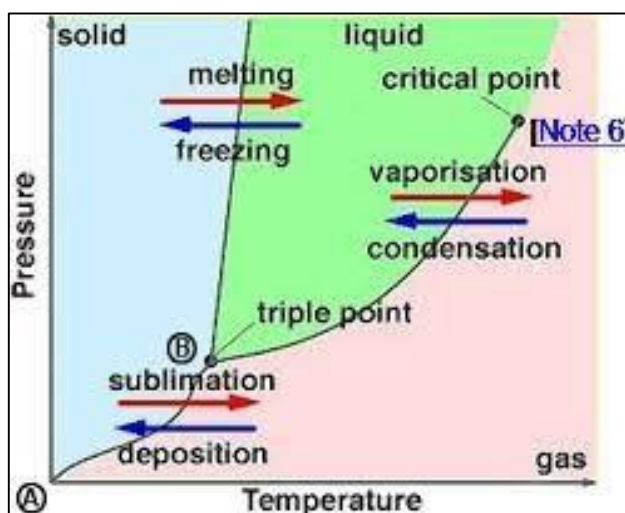
As the temperature of a liquid or solid increases its vapor pressure also increases. Conversely, vapor pressure decreases as the temperature decreases.

Factors That Affect Vapor Pressure

1. **Surface Area:** The vapor pressure is the equilibrium pressure where the rate of evaporation is equal to the rate of condensation. Since the scaling factor is the same, the vapor pressure is independent of the surface area.
2. **Types of Molecules:** the types of molecules that make up a solid or liquid determine its vapor pressure. If the intermolecular forces between molecules are:
 - relatively strong, the vapor pressure will be relatively low.
 - relatively weak, the vapor pressure will be relatively high.
3. **Temperature:** at a higher temperature, more molecules have enough energy to escape from the liquid or solid. At a lower temperature, fewer molecules have sufficient energy to escape from the liquid or solid.
4. **Intermolecular Forces:** Those liquids in which the intermolecular forces are weak shows high vapour pressure.

5. Sublimation critical point:

Sublimation is the change of state from a solid to a gas without passing through the liquid state. Carbon dioxide is an example of a material that easily undergoes sublimation.



Phase Diagram: It is a representation of the states of matter: Solid, Liquid or gas as a function of temperature and pressure

The temperature at which the vapor pressure of the solid phase of a compound is equal to the total pressure of the gas phase in contact with it; analogous to the boiling point of a liquid.

Phase Rule: Phase rule is a rule relating the possible numbers of phases, constituents, and degrees of freedom in a chemical system. This Rule was proposed by J. Willard Gibbs in 1876.

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The phase can be defined as *any homogeneous part of a system having all the physical and chemical properties. The properties are identical throughout.* A system may consist of one phase or more than one phase.

(1) A system containing only liquid water is a single-phase or single-phase system ($P = 1$)

(2) A system containing liquid water and steam (a gas) is a two-phase or two-phase systems ($P = 2$).

(3) A system containing liquid water, steam and solid ice is a three-phase or three-phase system. For a system at equilibrium the phase rule relates:

$$P + F = C + 2$$

Where

P = number of phases that can coexist

F = number of components making up the phases, and

F = number of independent variables or degrees of freedom.

6. Eutectic mixtures:

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. 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.

Eutectic mixture formation is usually, governed by following factors:

(a) The components must be miscible in liquid state and mostly immiscible in solid state,

(b) Intimate contact between eutectic forming materials is necessary for contact induced melting point depression,

(c) The components should have chemical groups that can interact to form physical bonds such as intermolecular hydrogen bonding etc.,

(d) The molecules which are in accordance to modified VanHoff's equation can form eutectic mixtures.

Applications of Eutectic Mixtures in Pharmaceutical Industry

1. During pre formulation stage, compatibility studies between APIs and excipient play a crucial role in excipient selection.

2. Testing for eutectic mixture formation can help in anticipation of probable physical incompatibility between drug and excipient molecules.

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3. 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.

4. 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.

5. 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 [4]. This knowledge could be used to identify compounds like Ergotamine, Allobarbitol etc. (Table 2). The listed drugs can be distinguished by their tendency to form eutectic mixtures with Benzanilide.

S No	Eutectic Components (a,b)	Ratio	Tm °C (a)	Tm °C (b)	Tm °C (e)	Challenges	Findings
1	Curcumin, Nicotinamide [5]	1:2	181.4	128.3	110.5	Oral route- Low solubility, poor oral bioavailability	10-fold faster IDR and 6-times higher AUC compared to crystalline curcumin.
2	Ibuprofen, Thymol [1]	2:3	76.0	52.0 [6]	32.0	Transdermal Route- Limited ability to penetrate the skin	A flux of 150 mg/ cm / h, 5.9 times the flux from a saturated aqueous solution with thymol pretreated skin and 12.7 times the flux from a saturated aqueous solution across non-pretreated skin
3	Genistein, PEG 460 [7]	1:24	305.0	2.0	0.2	Parenteral Route- Low aqueous solubility, thus formulation difficulty.	Could help in solubilization of geinstein crystals for injection development.
4	Borneol, Menthol (Active 125I-cobrotoxin and eutectic mixture mixed) [8]	1:3	-	-	-	Nasal Route- Blood Brain Barrier	The eutectic mixture of Borneol Menthol, enhanced formulation and passage of active across the blood brain barrier.
5	Menthol and Poloxamer 188, Ibuprofen (Liquid-gel like Suppository) [9]	1:9	-	-	-	Rectal Route- Low bioavailability	Higher AUC as compared to a solid suppository.

Tm: Melting point temperature; E: Eutectic Mixture; IDR: Intrinsic Dissolution Rate; AUC: Area Under Curve; PEG: Poly Ethylene Glycol

Applications of eutectic mixtures in formulation development.

S No	Drug	Tm°C	Tm(Eutectic)°C
1	Allobarbitol	173.0	144.0
2	Ergotamine	172.0-174.0	135.0
3	Imipramine HCl	172.0-174.0	109.0

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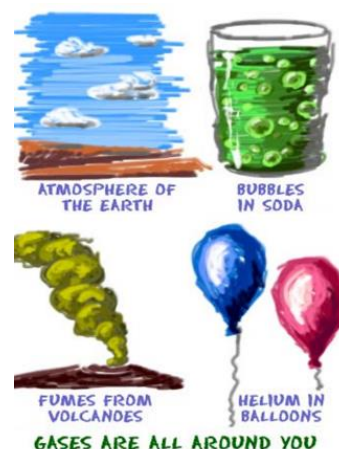
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7. Gases:

Gases are compressible fluid and has no definite shape

Owing to vigorous and rapid motion and resultant collisions, gas molecules travel in random paths and collide not only with one another but also with the walls of the container in which they are confined. Hence, they exert a *pressure*—a force per unit area—expressed in dynes/cm². Pressure is also recorded in atmospheres or in millimeters of mercury because of the use of the barometer in pressure measurement. Another important characteristic of a gas, its *volume*, is usually expressed in liters or cubic centimeters (1 cm³ = 1 mL). The temperature involved in the gas equations is given according the absolute or Kelvin scale. Zero degrees on the centigrade scale is equal to 273.15 Kelvin (K).



▪ Properties of Gases:

- 1) A sample of gas assumes both the shape and volume of the container.
- 2) Gases are compressible.
- 3) The densities of gases are much smaller than those of liquids and solids and are highly variable depending on temperature and pressure.
- 4) Gases form homogeneous mixtures (solutions) with one another in any proportion.

▪ The Gas Laws

1) *Boyle's law*: This law states that *the pressure of a fixed amount of gas at a constant temperature is inversely proportional to the volume of the gas.*

$$P \propto \frac{1}{V} \quad \text{Pressure is inversely proportional to the volume.}$$

2) *Charles Law*: This law states that the pressure of a fixed amount of gas at a constant At a fixed pressure, the volume of a gas is proportional to the temperature of the gas."

$$V \propto T$$

3) *Gay-Lussac's law*: This law is a special case of ideal gas law. This law applies to ideal gases held at a constant volume allowing only the pressure and temperature to change.

$$P_1/T_1 = P_2/T_2.$$

4) *Avogadro law*: This law states that the volume of a sample gas is directly proportional the number of moles in the sample at constant temperature and Pressure.

$$V \propto n$$

or

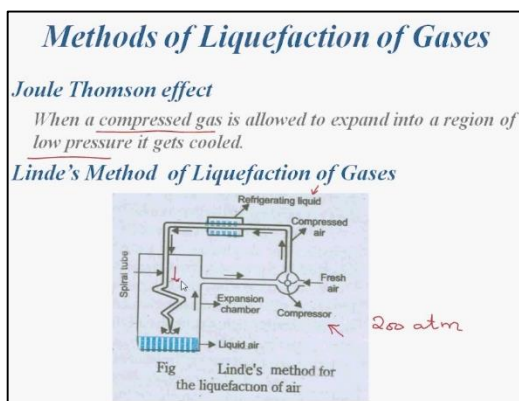
$$\frac{V_1}{n_1} = \frac{V_2}{n_2}$$

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- **Kinetic Molecular Theory of Gases:** The basic assumptions of the Kinetic Molecular Theory are
 1. The volume occupied by the individual particles of a gas is negligible compared to the volume of the gas itself.
 2. The particles of an ideal gas exert no attractive forces on each other or on their surroundings.
 3. Gas particles are in a constant state of random motion and move in straight lines until they collide with another body.
 4. The collisions exhibited by gas particles are completely elastic; when two molecules collide, total kinetic energy is conserved.
 5. The average kinetic energy of gas molecules is directly proportional to absolute temperature only; this implies that all molecular motion ceases if the temperature is reduced to absolute zero.
- **Liquefaction of Gases:** When pressure on a gas is increased, its molecules closer together, and its temperature is reduced, which removes enough energy to make it change from the gaseous to the liquid state.



8. Aerosols – inhalers

An aerosol is a suspension of fine solid particles or liquid droplets, in air or another gas. Aerosols can be natural or anthropogenic. Examples of natural aerosols are fog, dust, forest exudates and geyser steam. Examples of anthropogenic aerosols are haze, particulate air pollutants and smoke

Inhalers: An inhaler is a device holding a medicine that you take by breathing in (inhaling). Inhalers are often used to treat chronic obstructive pulmonary disease (COPD). They are three types: Metered-dose inhaler, Dry powder inhalers, Nebulizers.



Metered-dose inhaler



Dry powder inhalers



Nebulizers

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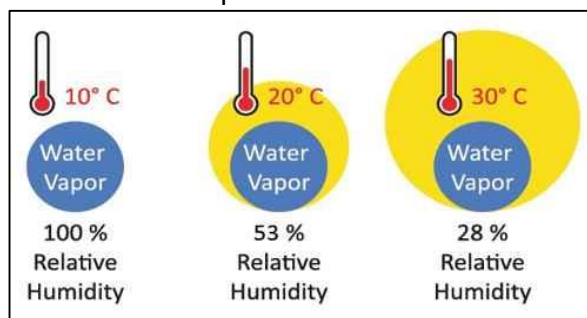


Gases can be liquefied under high pressures in a closed chamber as long as the chamber is maintained below the critical temperature. When the pressure is reduced, the molecules expand and the liquid reverts to a gas. This reversible change of state is the basic principle involved in the preparation of pharmaceutical aerosols. In such products, a drug is dissolved or suspended in a *propellant*, a material that is liquid under the pressure conditions existing inside the container but that forms a gas under normal atmospheric conditions. The container is so designed that, by depressing a valve, some of the drug-propellant mixture is expelled owing to the excess pressure inside the container. If the drug is nonvolatile, it forms a fine spray as it leaves the valve orifice; at the same time, the liquid propellant vaporizes off.

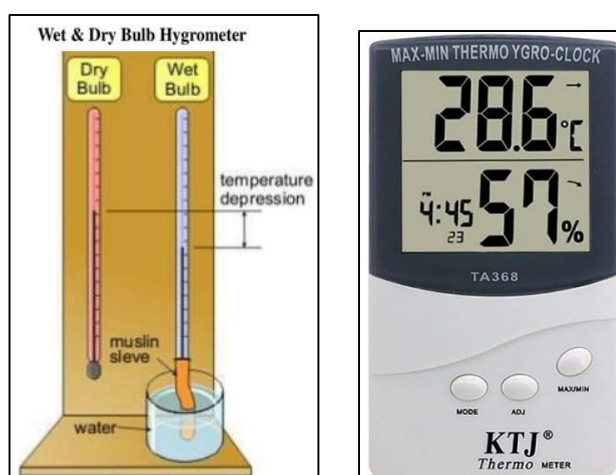


9. Relative humidity:

Is a ratio, expressed in percent, of the amount of atmospheric moisture present relative to the amount that would be present if the air were saturated.



Since the latter amount is dependent on temperature, relative humidity is a function of both moisture content and temperature. Relative Humidity is derived from the associated Temperature and Dew Point for the indicated hour.



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10. Liquid complexes:

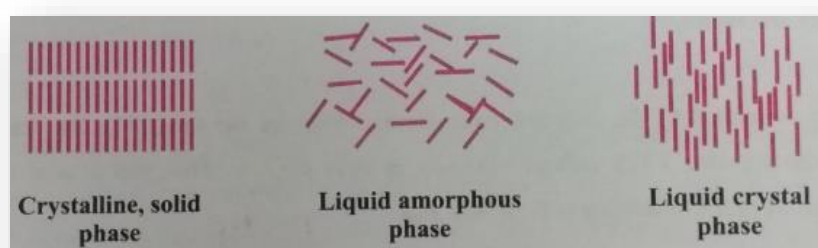
Complex fluids are binary mixtures that have a coexistence between two phases: solid–liquid (suspensions or solutions of macromolecules such as polymers), solid–gas (granular), liquid–gas (foams) or liquid–liquid (emulsions). They exhibit unusual mechanical responses to applied stress or strain due to 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.

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.



11. Liquid crystals:

A fourth state of matter is called liquid crystal state or mesophase or (mesomorphic phases) It is the state that occurs between a solid & a liquid. It possess characteristics of both liquids & crystalline solids. In crystalline solid state the molecules are held in position by intermolecular force. The particles in a solid move but cannot cross each other because the attractions of neighbouring atoms or molecules are too strong to overcome. In the liquid state, the molecules move to random positions. But in the liquid crystal state, the increased molecular motion overcomes the weaker forces, but the molecule remains bound by stronger forces. This produces a molecular arrangement where the molecule is layered but within each layer, the molecules are arranged in a random position. The molecule can slide one around the other, and layers can slide over one another. This molecular mobility generate fluidity in liquid crystal state.

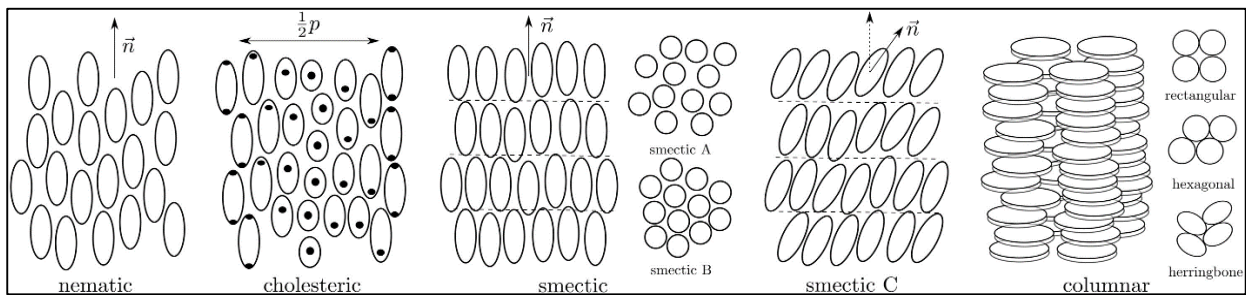


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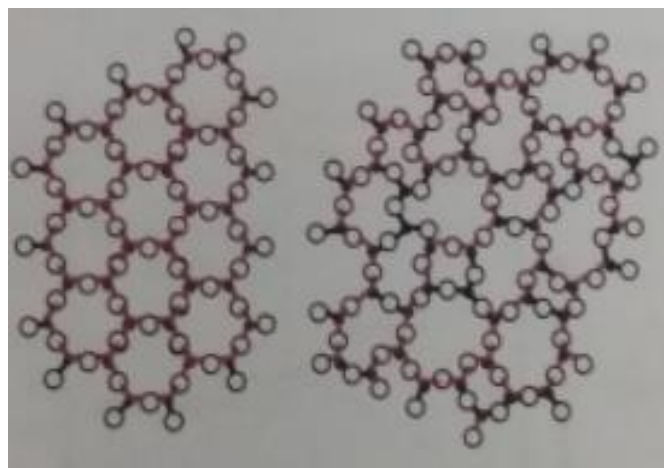


- **Types of Liquid crystals :** Liquid crystals are
 - A. Thermotropic Liquid Crystals:** Liquid crystals are said to be thermotropic if liquid crystalline properties depend on the temperature.
 - a. *Nematic Liquid Crystals:* Here the molecules (mesogens) have no positional order, but they have long-range orientational order
 - b. *Smectic Liquid Crystals:* In this, the mesogens have both positional order and orientational order.
 - c. *Cholestric liquid Crystals:* The cholestric phase can be defined as a special type of nematic liquid crystals in which thin layers of the parallel mesogens have their longitudinal axes rotated in adjacent layers at certain angle.
 - B. Lyotropic Liquid Crystals:** Liquid crystals which are prepared by mixing two or more substances of which one is a polar molecule, are known as lyotropic liquid crystals. Eg. Soap in



12. Glassy states:

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 supercooled liquids (e.g., rubber, leather, syrup).



Schematic two-dimensional illustration of the atomic arrangement in (1) crystal and (2) glass

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 glass 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.

13. Solid Crystalline:

The structural units of crystalline solids, such as ice, sodium chloride, and menthol, are arranged in fixed geometric patterns or lattices. Crystalline solids, unlike liquids and gases, have definite shapes and an orderly arrangement of units. Gases are easily compressed, whereas solids, like liquids, are practically incompressible. Crystalline solids show definite melting points, passing rather sharply from the solid to the liquid state. Crystallization, as is sometimes taught in organic chemistry laboratory courses, occurs by precipitation of the compound out of solution and into an ordered array. Note that there are several important variables here, including the solvent(s) used, the temperature, the pressure, the crystalline array pattern, salts (if crystallization is occurring through the formation of insoluble salt complexes that precipitate), and so on, that influence the rate and stability of the crystal (see the section Polymorphism) formation. The various crystal forms are divided into six distinct crystal systems based on symmetry. They are, together with examples of each, cubic (sodium chloride), tetragonal (urea), hexagonal (iodoform), rhombic (iodine), monoclinic (sucrose), and triclinic (boric acid). The morphology of a crystalline form is often referred to as its *habit*, where the crystal habit is defined as having the same structure but different outward appearance (or alternately, the collection of faces and their area ratios comprising the crystal).

The units that constitute the crystal structure can be atoms, molecules, or ions. The sodium chloride crystal, shown in Figure 2-6, consists of a cubic lattice of sodium ions interpenetrated by a lattice of chloride ions, the binding force of the crystal being the electrostatic attraction of the oppositely charged ions. In diamond and graphite, the lattice units consist of atoms held together by covalent bonds. Solid carbon dioxide, hydrogen chloride, and naphthalene form crystals

composed of molecules as the building units. In organic compounds, the molecules are held together by van der Waals forces, Coulombic forces, and hydrogen bonding, which account for the weak binding and for the low melting points of these crystals. Aliphatic hydrocarbons crystallize with their chains lying in a parallel arrangement, whereas fatty acids

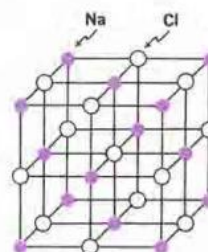


Fig. 2-6. The crystal lattice of sodium chloride.

crystallize in layers of dimers with the chains lying parallel or tilted at an angle with respect to the base plane. Whereas ionic and atomic crystals in general are hard and brittle and have high melting points, molecular crystals are soft and have relatively low melting points.

Metallic crystals are composed of positively charged ions in a field of freely moving electrons, sometimes called the *electron gas*. Metals are good conductors of electricity because of the free movement of the electrons in the lattice. Metals may be soft or hard and have low or high melting points. The hardness and strength of metals depend in part on the kind of imperfections, or *lattice defects*, in the crystals.

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Crystalline solids are falling on four categories:

Type of Solid	Forces holding particles together	Properties	Examples
Ionic	Ionic	High Melting Point, Brittle, Hard, Nonconductors as solid, good conductors as liquids or when dissolved in water.	NaCl, MgO
Molecular	Hydrogen Bonding, Dipole-Dipole, London Dispersion	Low Melting Point, Nonconductors	H ₂ , CO ₂
Metallic	Metallic Bonding	Variable Hardness and Melting Point (depending upon strength of metallic bonding), Good conductors as solids and liquids	Fe, Mg
Covalent Network	Covalent Bonding	High Melting Point, Hard, Nonconductors	C (diamond), SiO ₂ (quartz)

14. Amorphous:

Amorphous material is one kind of nonequilibrium material; its characteristic of atomic arrangement is more like liquid and has no long-range periodicity. The glass-forming ability of an alloy is closely related to its composition, and is quite different in various alloys. Generally, amorphous alloy can be produced by a rapid solidification method to freeze the liquid structure of the alloy melt, or other methods may be used that can mix atoms to achieve a disordered state. Amorphous materials have become one of the most actively researched fields. The deep theoretical understanding of the amorphization and nonequilibrium state guides and promotes research and development of amorphous materials. In this chapter, the atomic structure, formation criteria, and preparation methods of amorphous materials are summarized, and new progress in the formation and synthesis of bulk amorphous materials and bulk amorphous-based composites are briefly introduced.



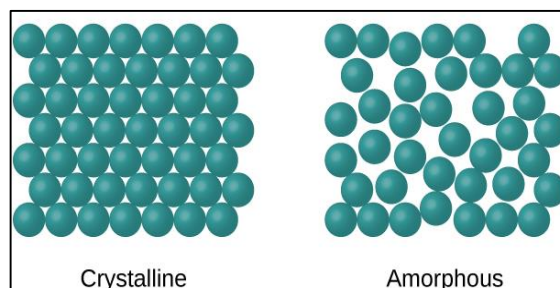
From the desk of **Abhijit Debnath**, Asst. Professor PDM University

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❖ What is the difference between glassy and amorphous?

Glassy systems feature the phenomenon of glass transition: transition from supercooled liquid --> amorphous solid (glass); however, all amorphous systems do not necessarily arise from such phenomenon. Consequently, all amorphous materials are not necessarily glasses.



15. Polymorphism

Polymorphism is the ability of solid materials to exist in two or more crystalline forms with different arrangements or conformations of the constituents in the crystal lattice. These polymorphic forms of a drug differ in the physicochemical properties like dissolution and solubility, chemical and physical stability, flowability and hygroscopicity. These forms also differ in various important drug outcomes like drug efficacy, bioavailability, and even toxicity. Polymorphic studies are important as a particular polymorph can be responsible for a particular property which might not be exhibited by any other form.

❖ Why does the amorphous form of drug have better bioavailability than crystalline counterparts?

Solubility depends on the formation of intermolecular hydrogen bonds between solvent molecules and the solute molecules. The crystalline form is more stable than the amorphous form and has a lower energy at the molecular level with stronger bonding (mostly ionic bonds) between molecules that require higher energy to break. So, higher solubility means higher dissolution rate and better bioavailability

Suggested Books For Reading:

- Physical Pharmacy by Alfred Martin
- Tutorial Pharmacy by Cooper and Gunn.
- Physical Pharmaceutics by C.V.S. Subramanyam
- Physical Pharmaceutics by Ramasamy C and ManavalanR.
- Test book of Physical Pharmacy, by Gaurav Jain & Roop K. Khar

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