STATES OF MATTER

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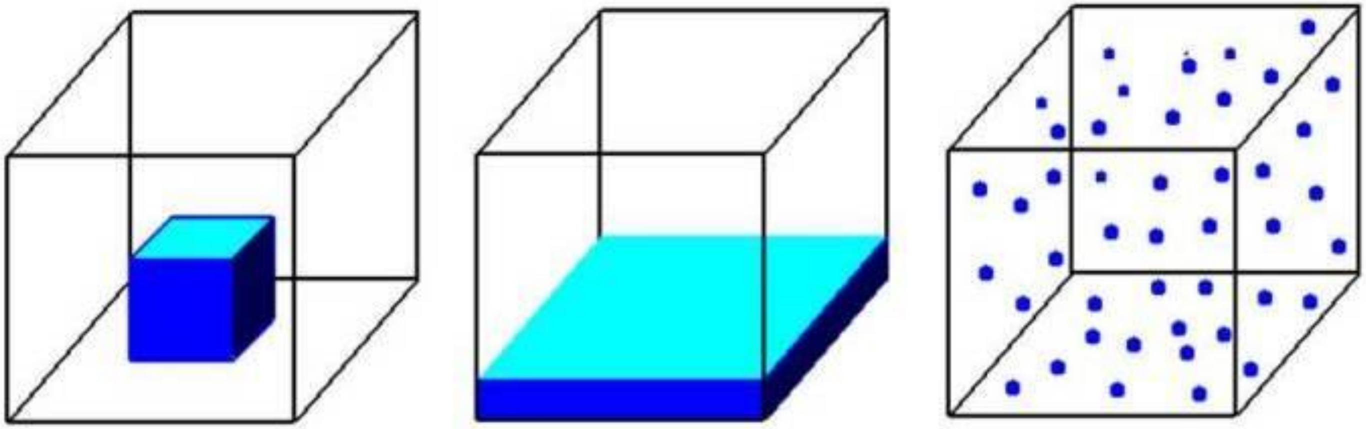
MATTER

MATTER

- Matter refers to all the substances that make up universe.
- Matter is made up of molecules, atoms and ions which are in turn made up of protons, neutrons and electrons.
- Atoms come together to form molecules, which are the building blocks for all types of matter.
- Both atoms and molecules are held together by a form of potential energy called chemical energy.
- Unlike kinetic energy, which is the energy of an object in motion, potential energy is the energy stored in an object.

STATES OF MATTER



Solid	Liquid	Gas
Holds Shape	Shape of Container Free Surface	Shape of Container
Fixed Volume	Fixed Volume	Volume of Container

STATES OF MATTER

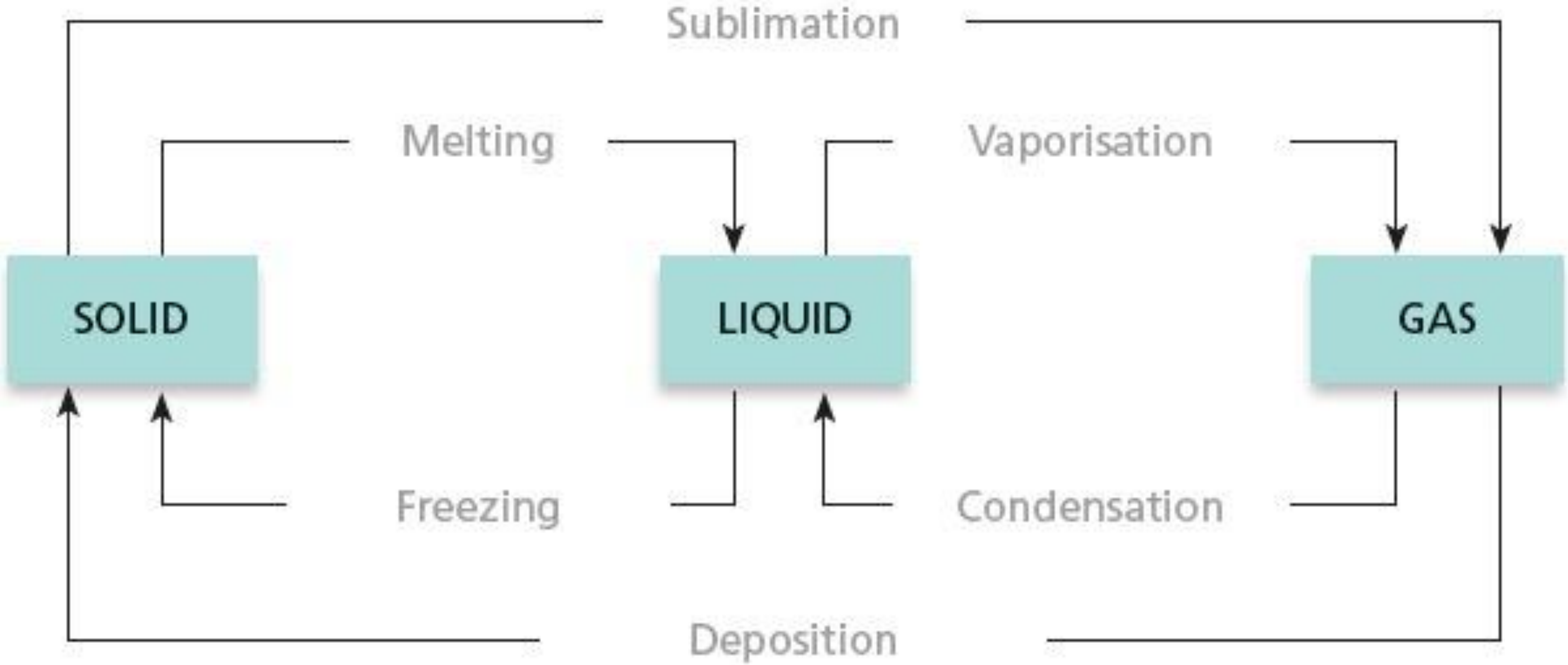
- The states of matter are the distinct physical forms that matter can take in most environments.
- The term phase is sometimes used as a synonym for state of matter, but a system can contain several immiscible phases of the same state of matter.
- Matter can exist in one of three main states: solid, liquid, or gas.
- Nearly every substance can exist as one of the three main states depending on its temperature and the pressure placed on it.

PROPERTY	SOLID	LIQUID	GAS
Packing	Very close	Loose	Far/ Very Far
Force of attraction	Strongest	Weaker	Negligible
Shape	Fixed	No	No
Volume	Fixed	Fixed	No
Compressibility	Negligible	Higher	Highest
Density	Highest	Less	Least
Kinetic Energy	Very small	Higher	Highest
Diffusion rate	Very Low	Higher	Highest
Example	Ice	Water	Water Vapor

CHANGES IN STATES OF MATTER

- Each of these three classical states of matter i.e. solid, liquid and gas can undergo transition directly into either of the other two classical states.
- The relationship between temperature and pressure and the three states of matter is easier to see when displayed in a phase diagram.
- Any change in phase is accompanied by the taking in or release of heat energy because, as change takes place, the attractive forces between molecules are being broken down or being formed.
- The Process of change of states of matter may commence by mechanisms like freezing, melting, deposition, sublimation, vaporization and condensation.

CHANGES IN STATES 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 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.

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

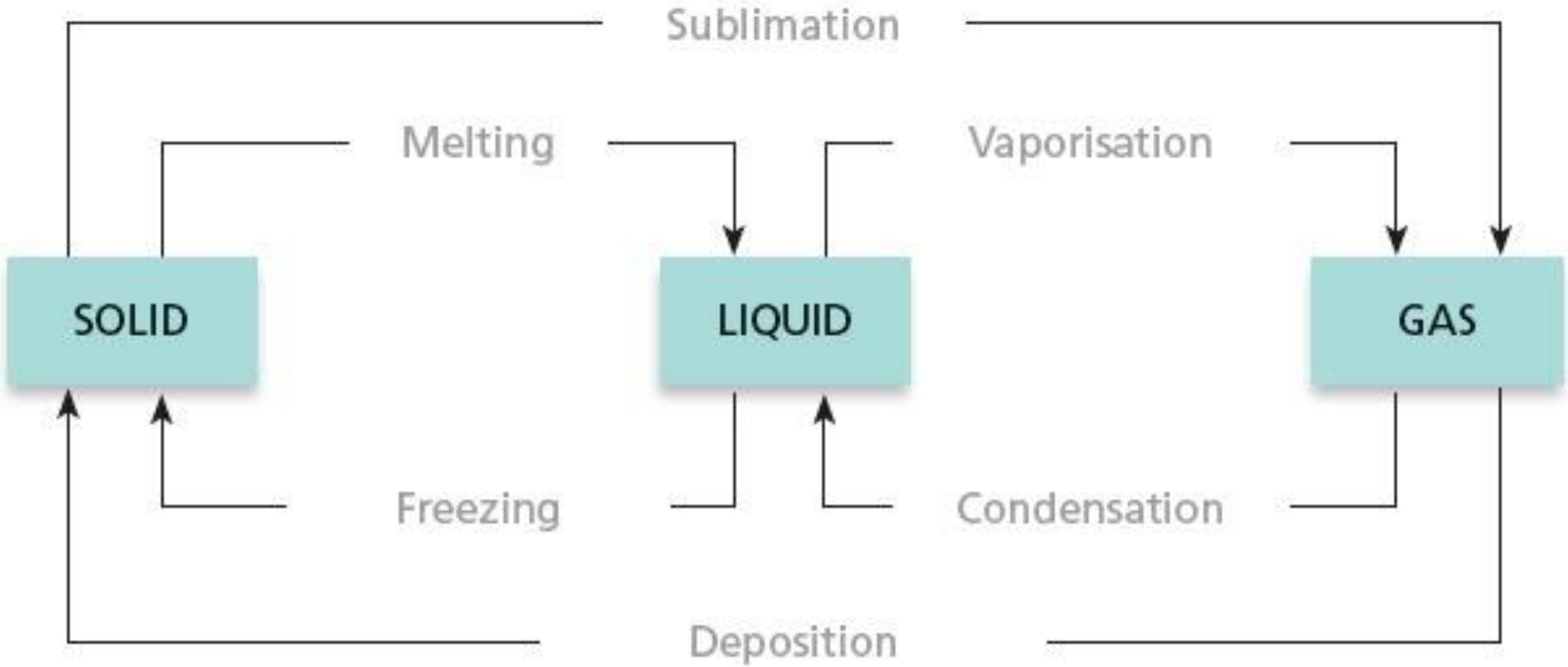
Vaporization: Vaporization of an element or compound is a phase transition from the liquid phase to vapor.

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

LATENT HEAT

- The latent heat is used in change of states of matter, such as from solid to liquid or from liquid to gas without rising in temperature.
- Latent heat is thermal energy released or absorbed, by a body or a thermodynamic system, during a constant-temperature process i.e. without change in temperature of the system. This happens while change of state of matter meaning a phase transition. Example: Melting of ice, boiling of water.
- The term was introduced around 1762 by British chemist Joseph Black.
- The particles of solid and liquid are bonded together with great force of attraction, because of which a matter exists in a particular state. When we supply heat to solid or liquid, the heat is used to break the force of attraction between the particles without affecting kinetic energy of particle hence causing the change of state.

HEAT ENERGY TAKEN FROM ENVIRONMENT →

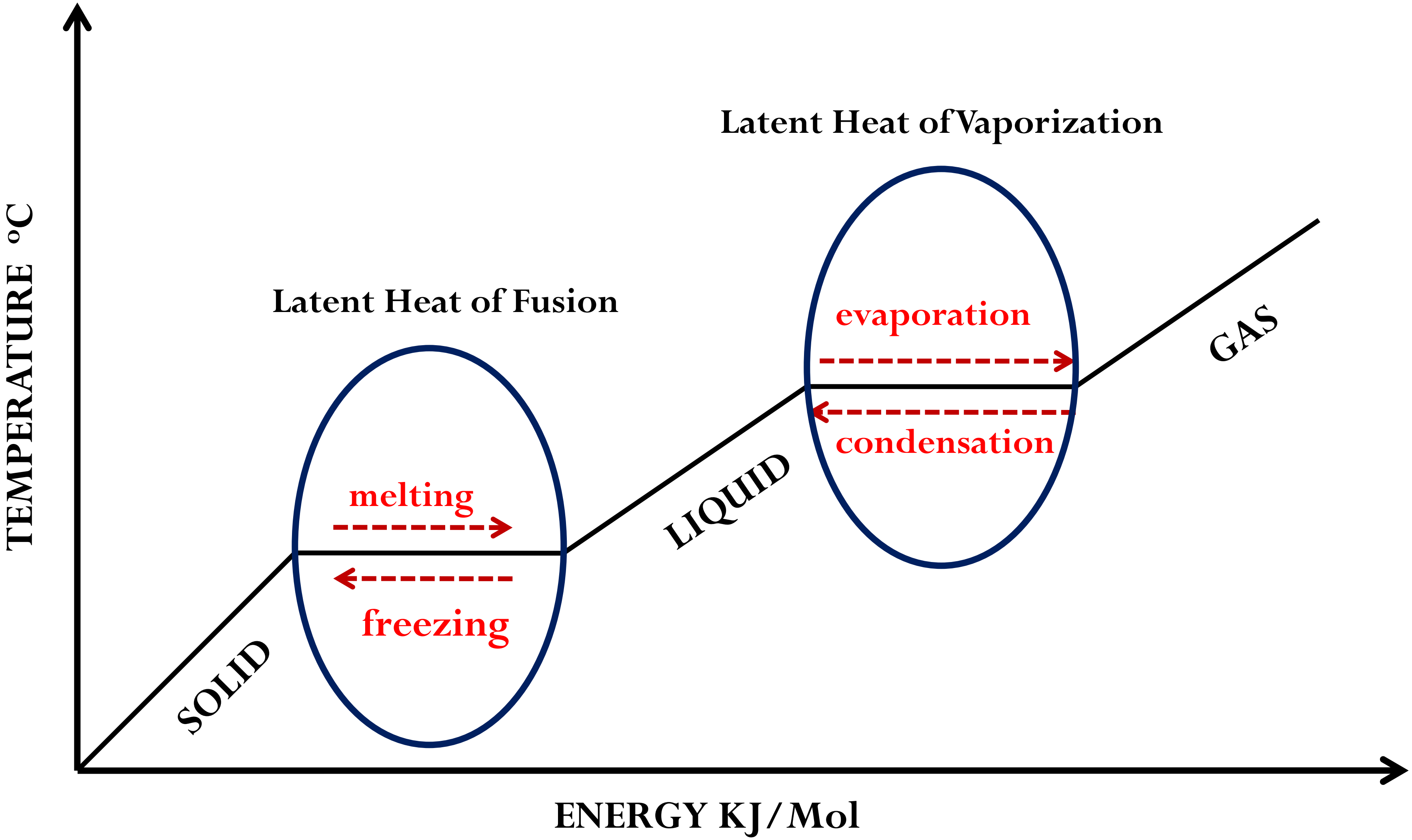


← **HEAT ENERGY RELEASED TO ENVIRONMENT**

continued…

- Sensible heat is a heat transfer that results in a temperature change in a body.
- The term ″sensible heat″ refer to types of heat transferred between a body and its surroundings. ″Sensible heat″ is ″sensed″ or felt in a process as a change in the body's temperature.
- A specific latent heat (L) expresses the amount of energy in the form of heat (Q) required to completely effect a phase change of a unit of mass (m), usually 1kg, of a substance as an intensive property $L = Q/m$

Types of Latent Heat



- **Latent heat of fusion:**
- The heat energy supplied per unit mass of a substance at its melting point to convert the state of the substance from solid to liquid is known as Latent heat of fusion.
- The regular structure of a crystalline solid is maintained by forces of attraction among its individual atoms, which oscillate slightly about their average positions in the crystal lattice. As the temperature increases, these motions become increasingly violent until, at the melting point, the attractive forces are no longer sufficient to maintain the stability of the crystal lattice. However, additional heat (the latent heat of fusion) must be added (at constant temperature) in order to accomplish the transition to the even more-disordered liquid state, in which the individual particles are no longer held in fixed lattice positions but are free to move about through the liquid.

- **Latent heat of vaporization:**
- The heat that a substance absorbs per unit mass at its boiling point to convert the phase of the substance from liquid to gas is the Latent heat of Vaporization.
- A liquid differs from a gas in that the forces of attraction between the particles are still sufficient to maintain a long-range order that endows the liquid with a degree of cohesion. As the temperature further increases, a second transition point (the boiling point) is reached where the long-range order becomes unstable relative to the largely independent motions of the particles in the much larger volume occupied by a vapor or gas. Once again, additional heat (the latent heat of vaporization) must be added to break the long-range order of the liquid and accomplish the transition to the largely disordered gaseous state.

SUBLIMATION

- Sublimation is the transition of a substance directly from the solid to the gas phase or vapor phase without passing through the intermediate liquid phase between the two.
- Sublimation refers to physical changes of transition and not to cases where solids convert into gas due to a chemical reaction. Because the physical change from a solid into a gas requires the addition of energy into the substance, it is an example of an endothermic change.
- It occurs when the particles of a solid absorb enough energy to completely overcome the force of attraction between them and escape into the vapor phase
- Since the process requires additional energy, it is an endothermic change. The enthalpy of sublimation (also called heat of sublimation) can be calculated by adding the enthalpy of fusion and the enthalpy of vaporization.
- The enthalpy of sublimation, or heat of sublimation, is the heat required to change one mole of a substance from solid state to gaseous state at a given combination of temperature and pressure, usually standard temperature and pressure (STP).
- The heat of sublimation is usually expressed in kJ/mol, although the less customary kJ/kg is also encountered.

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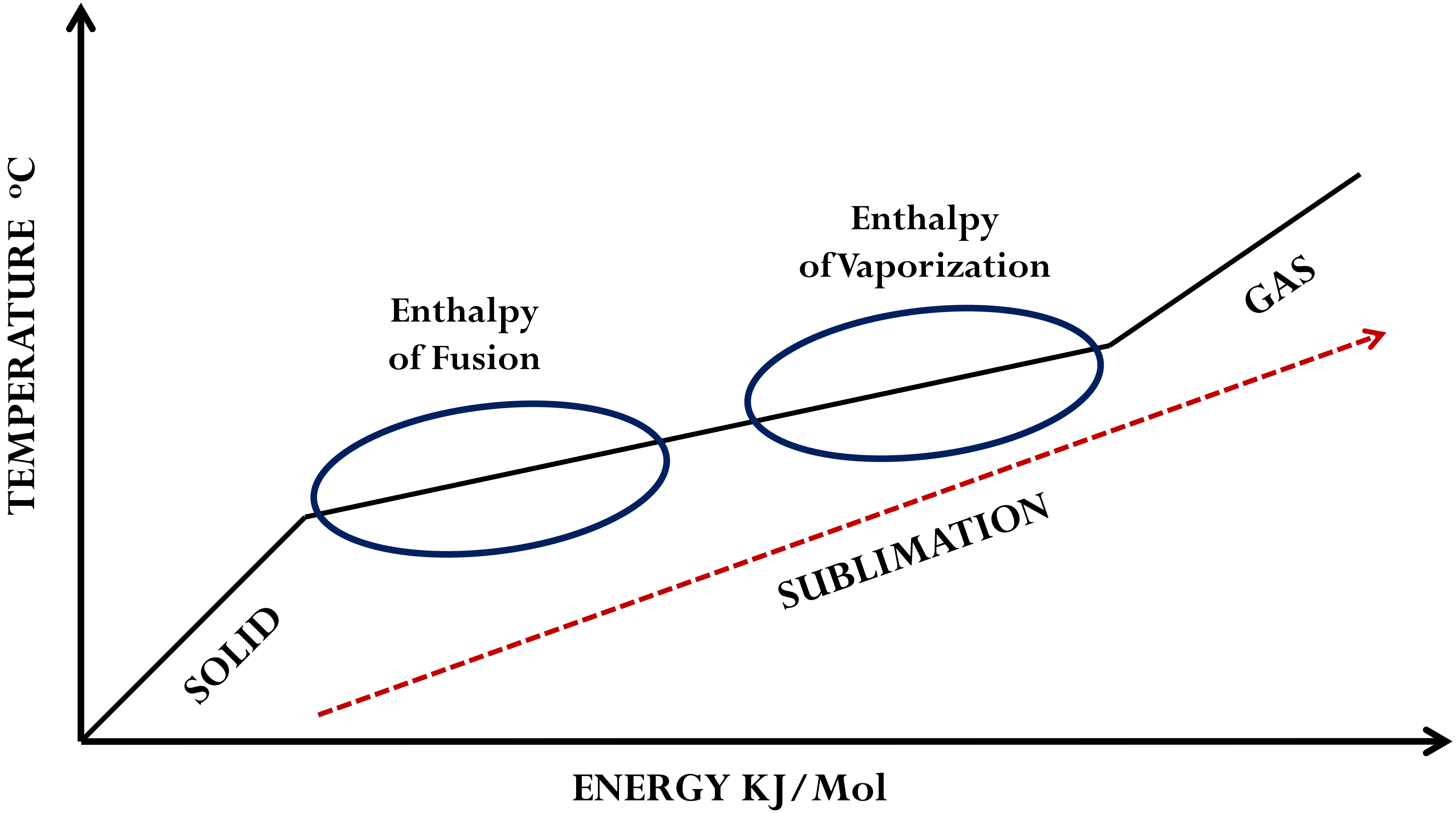
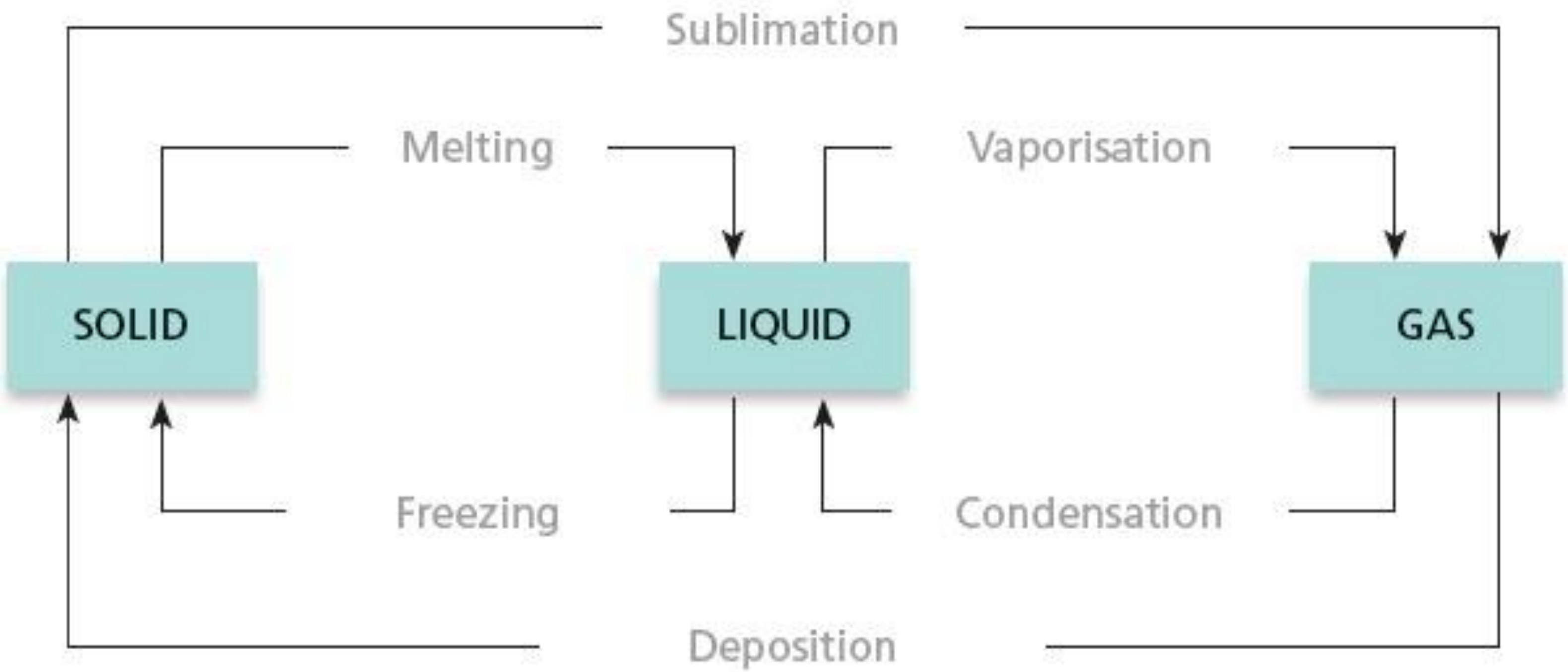
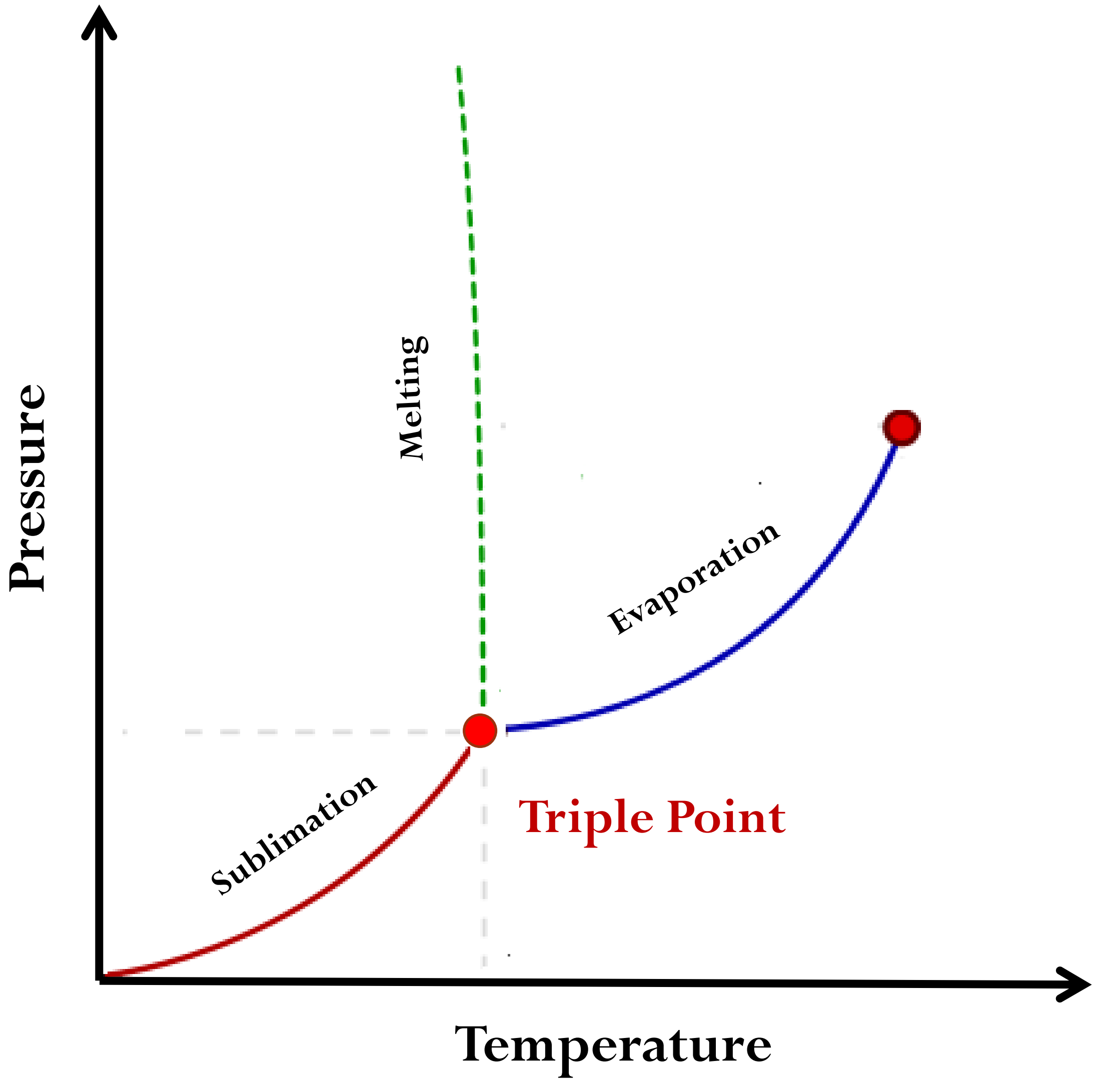

TEMPERATURE °C
Enthalpy
of Fusion
Enthalpy
of Vaporization
GAS
SOLID
SUBLIMATION
ENERGY KJ/Mol

CRITICAL POINT

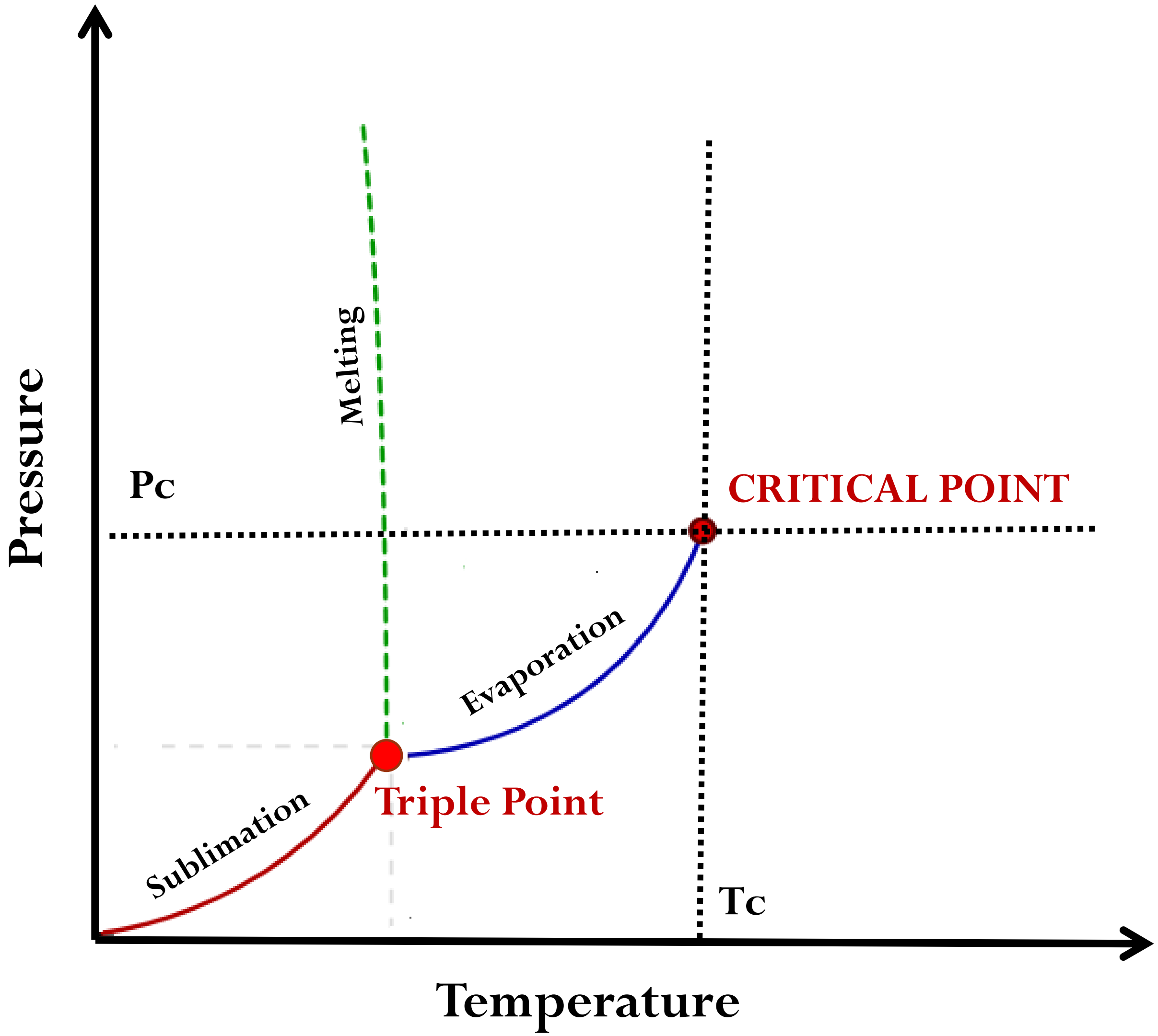
- The movement of molecules in matter changes and varies according to the variation in terms of temperatures and pressure.
- Critical point, in physics, the set of conditions under which a liquid and vapor become identical.



- The critical point is the end point of a phase equilibrium curve, defined by a critical pressure Pc and critical temperature Tc.
- This is best understood by observing Phase diagram. Phase diagrams illustrate the variations between the states of matter of elements or compounds as they relate to pressure and temperatures.
- A typical phase diagram has pressure (typically in atmospheres) on the y-axis and temperature (typically in degrees Celsius or Kelvin) on the x-axis.
- Phase diagram is a graphical representation of the physical states of a substance under different conditions of temperature and pressure.


Pressure
Melting
Evaporation
Sublimation
Triple Point
Temperature

- The movement of molecules in matter changes and varies according to the variation in terms of temperatures and pressure. As we cross the lines or curves on the phase diagram, a phase change occurs.
- In addition, two states of the substance coexist in equilibrium on the lines or curves.
- The point on a phase diagram at which the three states of matter: gas, liquid, and solid coexist is the triple point. At the triple point all three phases may be present in equilibrium.


Pressure
Melting
Pc
CRITICAL POINT
Evaporation
Triple Point
Sublimation
Tc
Temperature

continued…

- When the pressure is increased the movement of molecules in the substance will decrease because increases in terms of pressure hold the molecules in matter more tightly together; conversely, when the pressure is decreased, the movement of molecules in the substance will increase because decreases in terms of pressure allows the molecules in matter further away from each other.
- Similarly, when the temperature is increased the movement of molecules in the substance will increase because increases in temperature breaks the bonds and physical forces that hold the molecules tightly together; conversely, when the temperature is decreased the movement of molecules in the substance will decrease because decreases in temperature with the application of cold will hold the molecules more tightly together.

- Critical temperature (Tc) is the temperature above which gas can not be liquefied.
- Critical Pressure (Pc) is the minimum pressure required to liquefy the gas at critical temperature.
- Critical Volume (Vc) is the volume occupied by one mole of gas at critical temperature and critical pressure.

- At this point, there is no phase boundary.
- The study of critical phenomena is directed toward describing the various types of behavior near the critical points of these diverse and different systems with a single common theory.
- The critical point terminates the liquid/gas phase line and relates to the critical pressure, the pressure above which a supercritical fluid forms. Beyond the temperature of the critical point, the merged single phase is known as a supercritical fluid.

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- Above the critical Point there exists a state of matter that is continuously connected with both the liquid and the gaseous state. It is called as Supercritical Fluid.
- At Critical temperature and Pressure any gas behaves simillar to its liquid is said to be in critical state. This phenomenon is called as critical phenomenon.
- Critical Temperature (Tc), Critical Pressure (Pc) and Critical Volumes (Vc) are collectively called as Critical Constant.

GAS and FUNDAMENTAL PROPERTIES

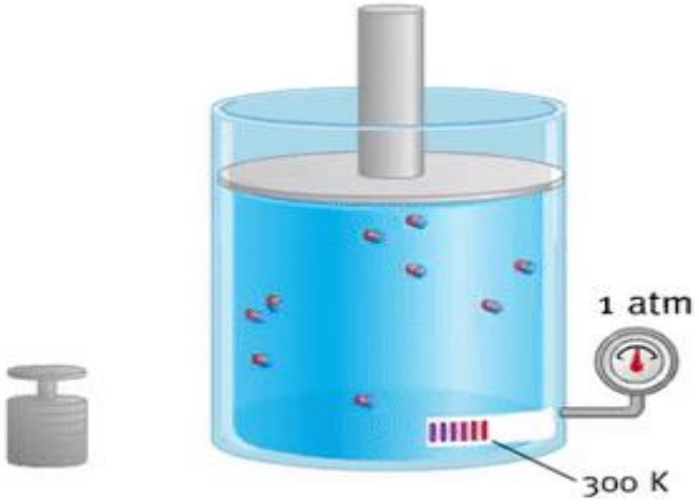
- Pressure (P)
- Temperature (T)
- Volume (V)
- Quantity (n)

Property	Notation	SI Unit
Pressure	**P**	**Pascal (Pa)**
Temperature	**T**	**Kelvin (K)**
Volume	**V**	**Litre (L)**
Quantity/Mass	**n**	**Mole (mol)**

PRESSURE

- When more gas particles enter a container, there is less space for the particles to spread out, and they become compressed. The particles exert more force on the interior volume of the container. This force is called pressure.

PRESSURE

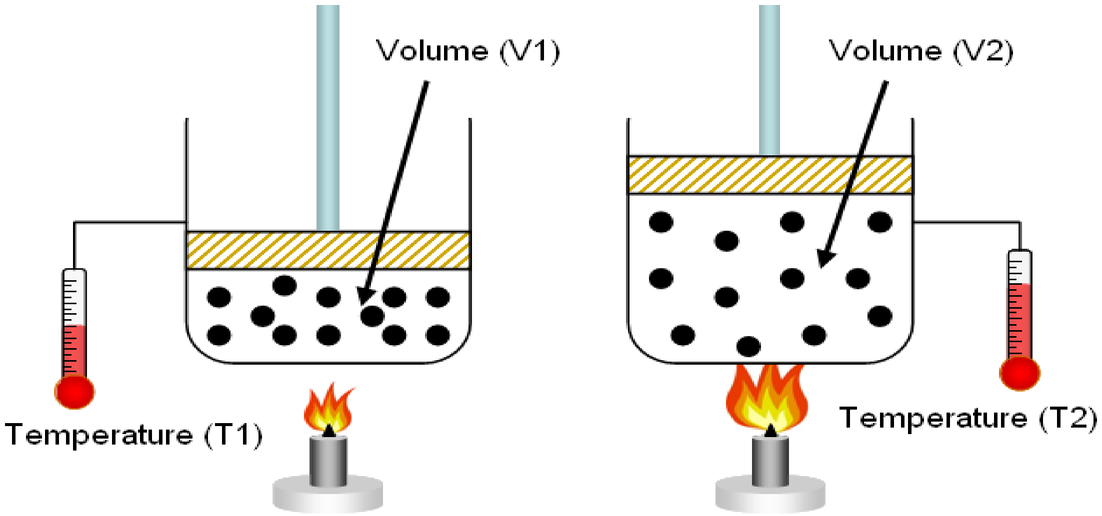


When pressure is applied on gas molecule stored in closed container the spaces between gas molecules will reduce and each molecule will come in close proximity of one another.

TEMPERATURE

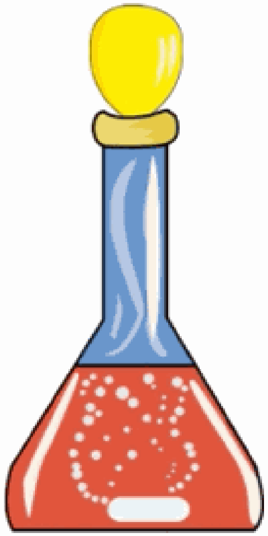
- When temperature is applied to gas dissolved the amount of energy used by the gas to escape from the solution form. The kinetic energy so generated reduces the adhesive forces between gas and liquid thus resulting into escaping of gas

TEMPERATURE



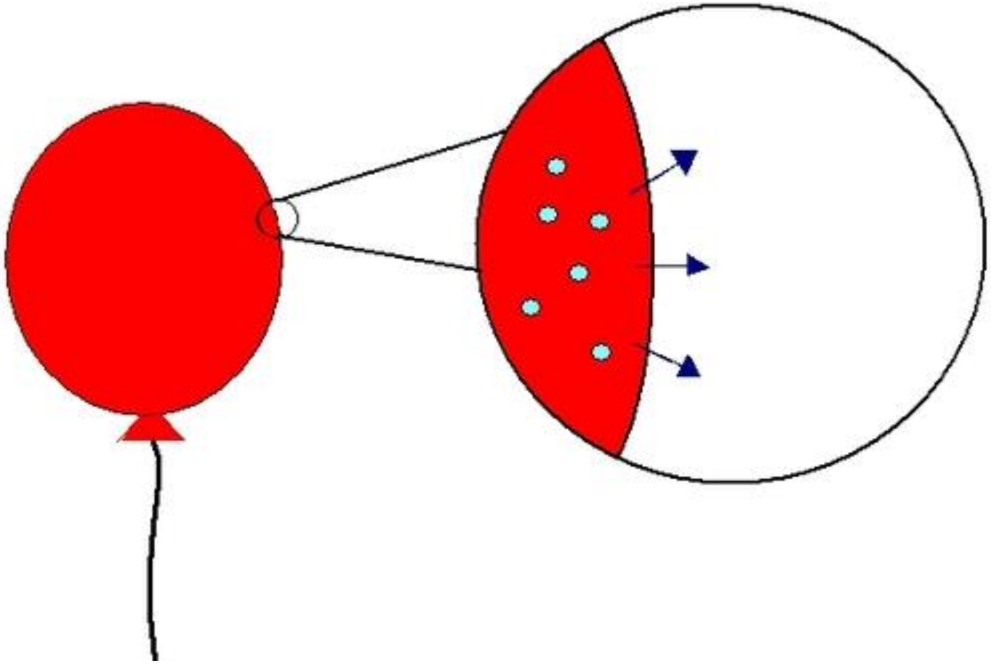
- When temperature is applied to pure gas in closed container the gas molecule will move with great energy. The fixed volume of closed container will not allow gas to escape from the container and thus moving gas will collide with each other and on wall of container.
- The pressure on wall of container may lead to explosion of container

VOLUME



- Gas Occupies total volume of container
- Volume changes with pressure and temperature.
- Gas volumes are usually measured in multiples of cubic feet (ft^3) or cubic meters (m^3).
- Volumes of gas are often measured in milliliters.
- One cubic centimeter of water (1 ml) has a mass of 1 gram.

QUNATITY

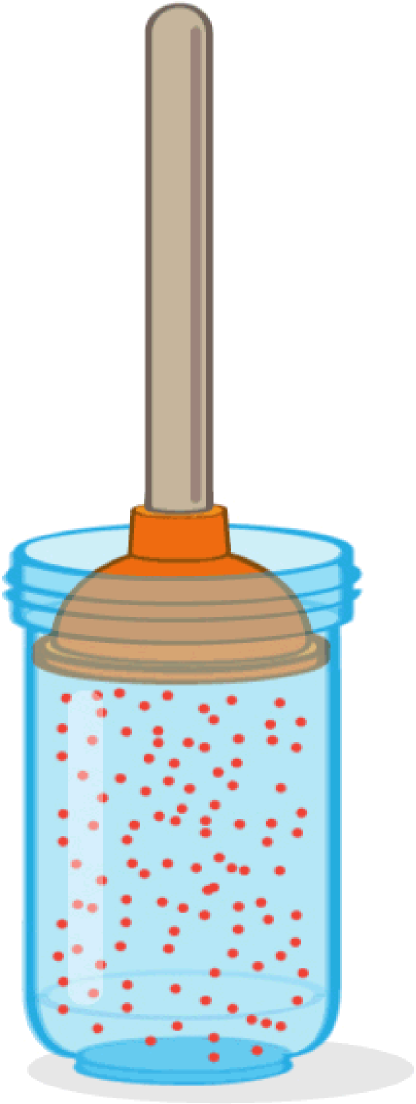


- The number of moles of gas can occupy the volume of container.
- If the amount of gas in a container is increased, the volume increases. If the amount of gas in a container is decreased, the volume decreases.

GAS LAWS

- **Gas Laws -** The relationship among the fundamental properties of gas
- **Empirical gas laws -** When two properties are observed at a time while holding two other constant.

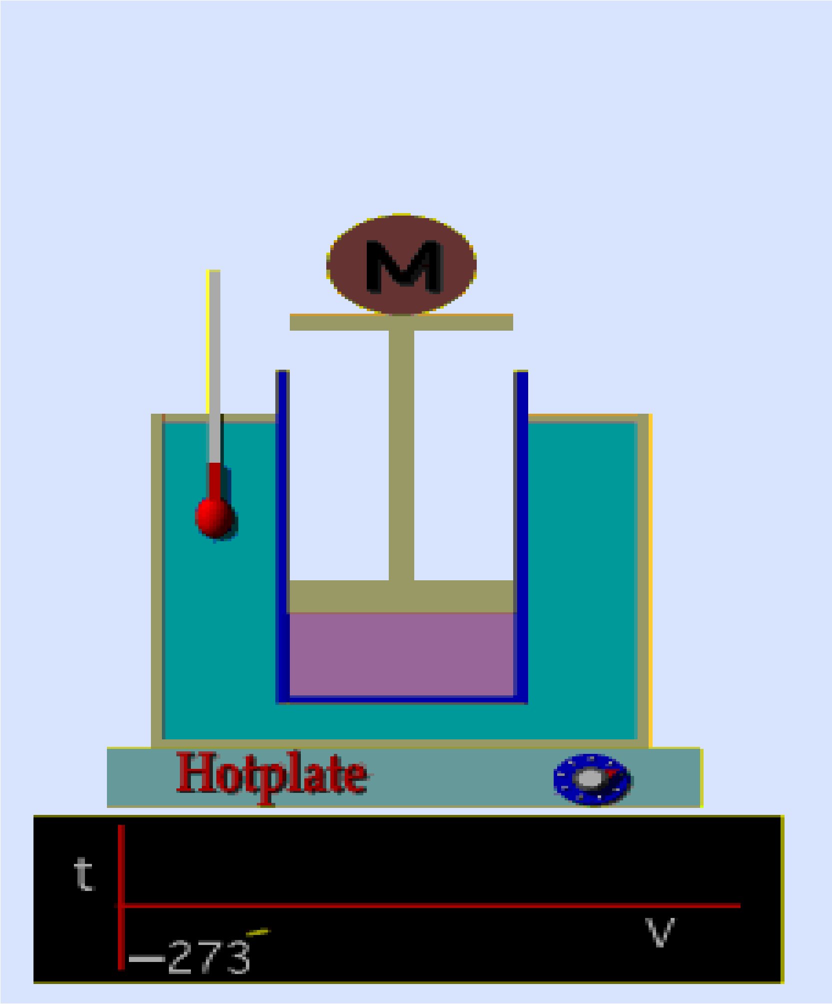
BOYLE's LAW



- Robert Boyle, in 1662 states that the pressure of a fixed amount of gas at a constant temperature is inversely proportional to the volume of the gas.

$$P \propto \frac{1}{V}$$

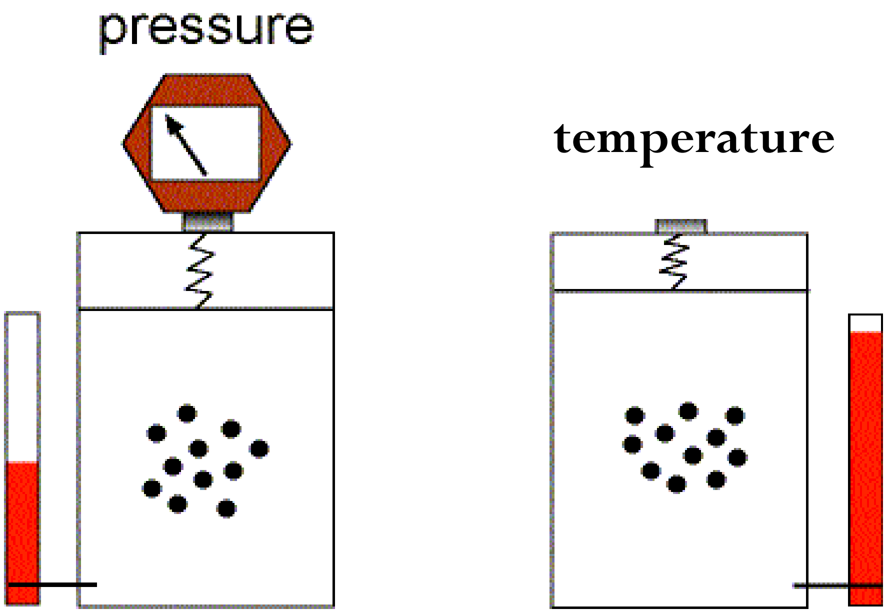
CHARLE's LAW



- Jacque Charles, in 1787 states that the volume of a fixed amount of gas at a constant pressure is directly proportional to the absolute temperature.

$$V \propto T$$

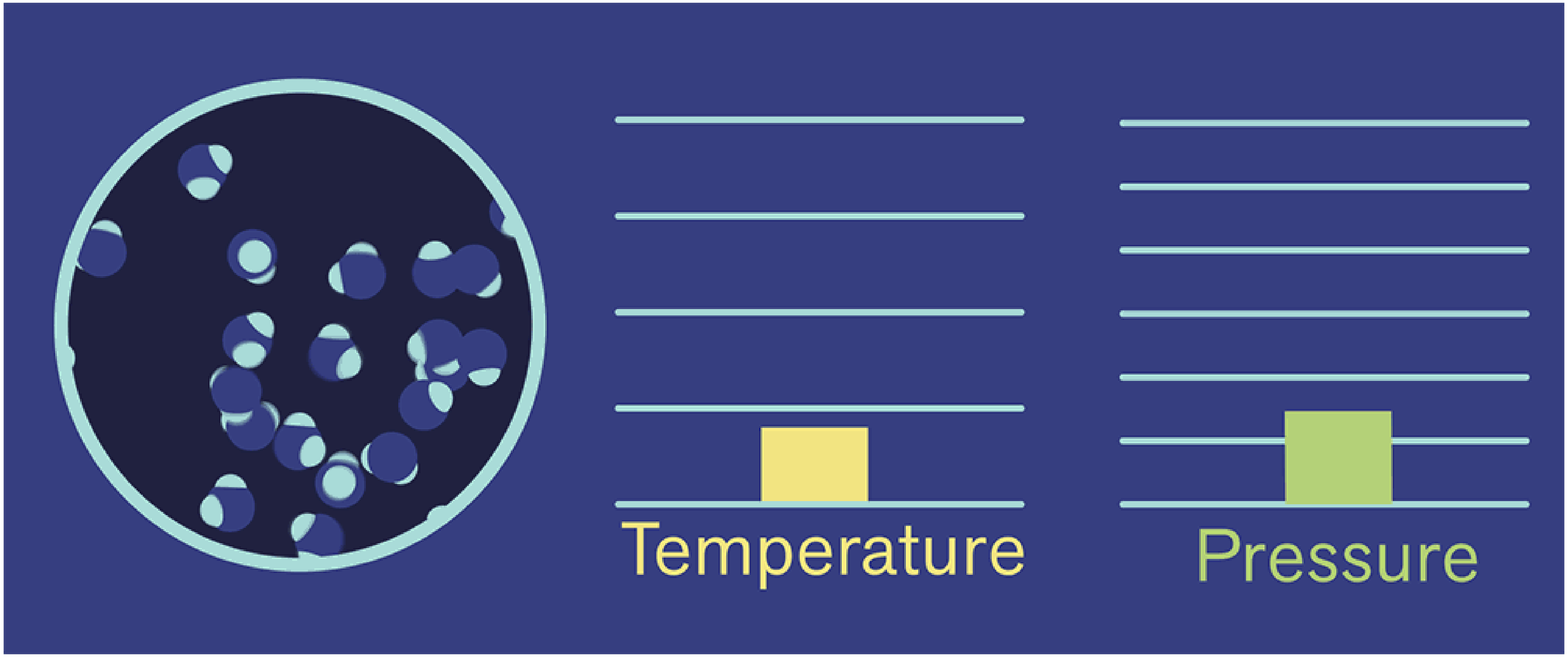
COMBINED GAS LAW



- According to combined gas law for fixed mass of gas, the volume is directly proportional temperature and inversely proportional to pressure

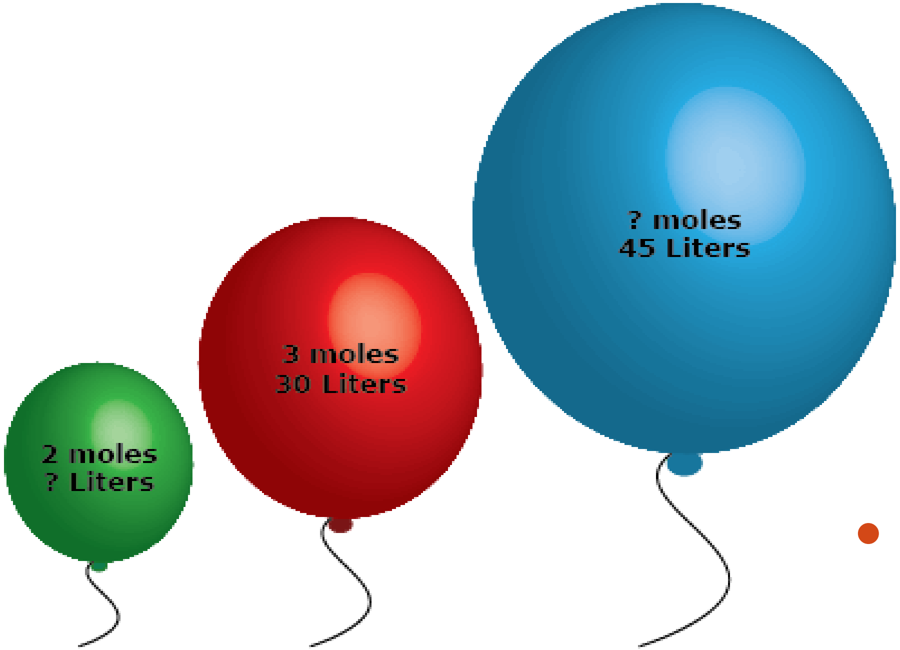
$$V \propto \frac{T}{P}$$

GAY LUSSAC's LAW



- Joseph Louis Gay-Lussac in 1802 state that the pressure of fixed mass of gas at constant volume is directly proportional to the absolute temperature. $P \propto T$

AVOGADRO’s LAW



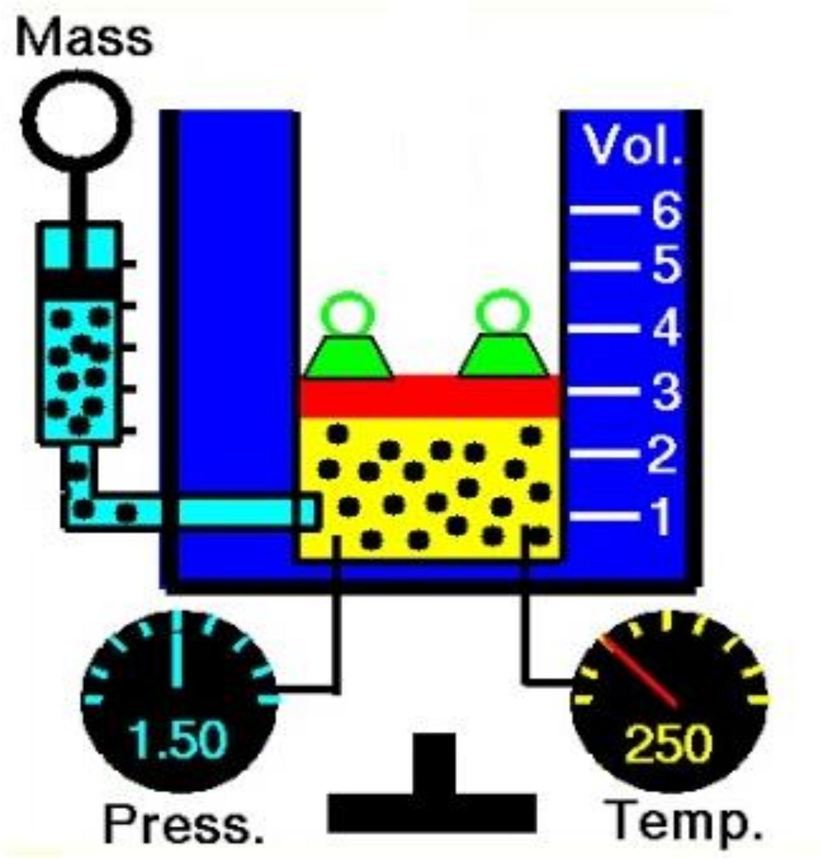
- Amedeo Avogadro in 1811 state that at constant temperature and pressure fixed mass of gas is directly proportional to volume.

$V \propto n$

SUMMARY

Law	Relating Properties	Constant	Expression
Boyle's Law	Pressure Volume	Temperature Quantity	$P \propto \frac{1}{V}$
Charle's Law	Temperature Volume	Pressure Quantity	$V \propto T$
Gay Lussac's Law	Pressure Temperature	Volume Quantity	$P \propto T$
Avogadro's Law	Volume Quantity	Pressure Temperature	$V \propto n$

IDEAL GAS EQUATION



- Ideal gas law states that, the volume of given amount of gas is directly proportional to number of moles of gas and it absolute temperature and inversely proportional to the pressure.

$$V \propto \frac{nT}{P}$$

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$$V = R\,\frac{nT}{P}$$

$$PV = nRT$$

- The equation PV = nRT is called as Ideal gas equation.
- The gas that obeys ideal gas equation is called as Ideal gasses and the gas which fails to obey the ideal gas equation are termed as non ideal gasses or real gasses.
- The extent to which real gas departs from ideal behavior is depicted in terms of compressibility factor (Z)

$$Z = \frac{PV}{RT}$$

- For ideal gas Z = 1, therefore the deviation from ideal behavior will be determined by the value of Z being less or great than 1

VAN DER WAAL’s EQUATION

- Real gas is composed of finite volume of particles that attracts one another. Therefore according to Van der Waals pressure and volume need to be corrected and so as to modify ideal gas equation to make it applicable.
- According to Van der Waal

- The molecule in gas posses no volume
- There are no intermolecular attraction

∴ After correcting pressure and correcting volume in ideal gas equation it becomes

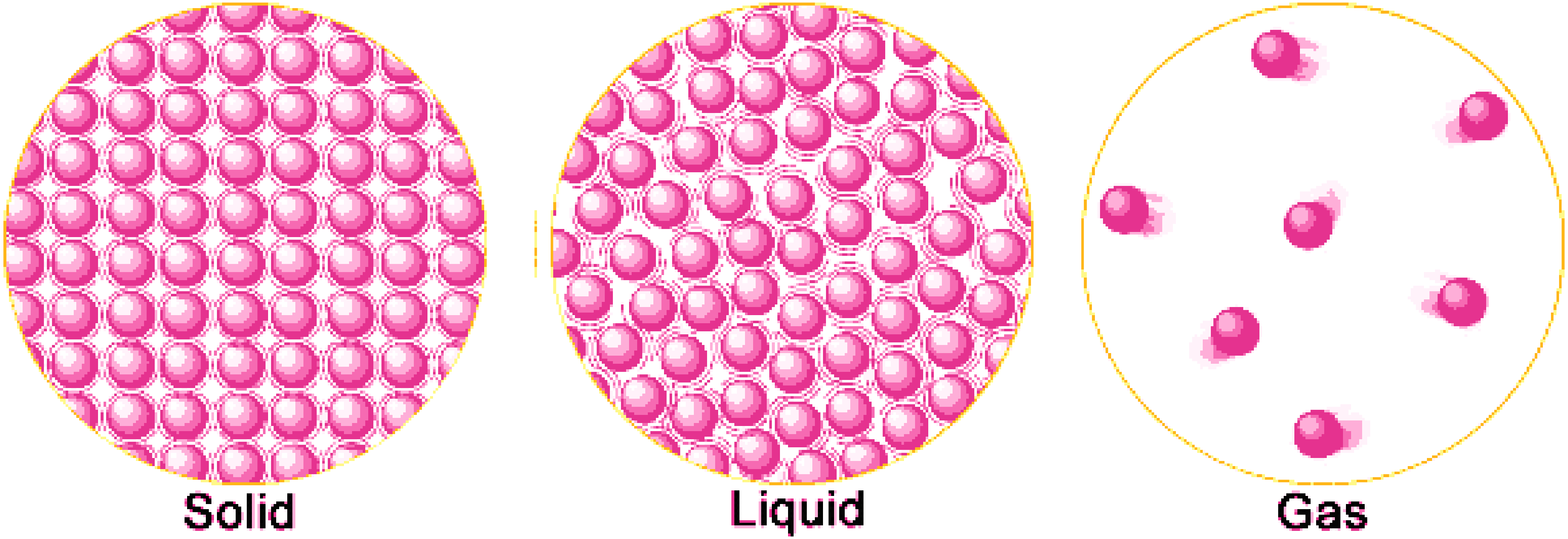
$$\left(P + \frac{an^2}{V^2}\right)(V - nb) = nRT$$

- The equation 11 is called as Van der Wall’s equation

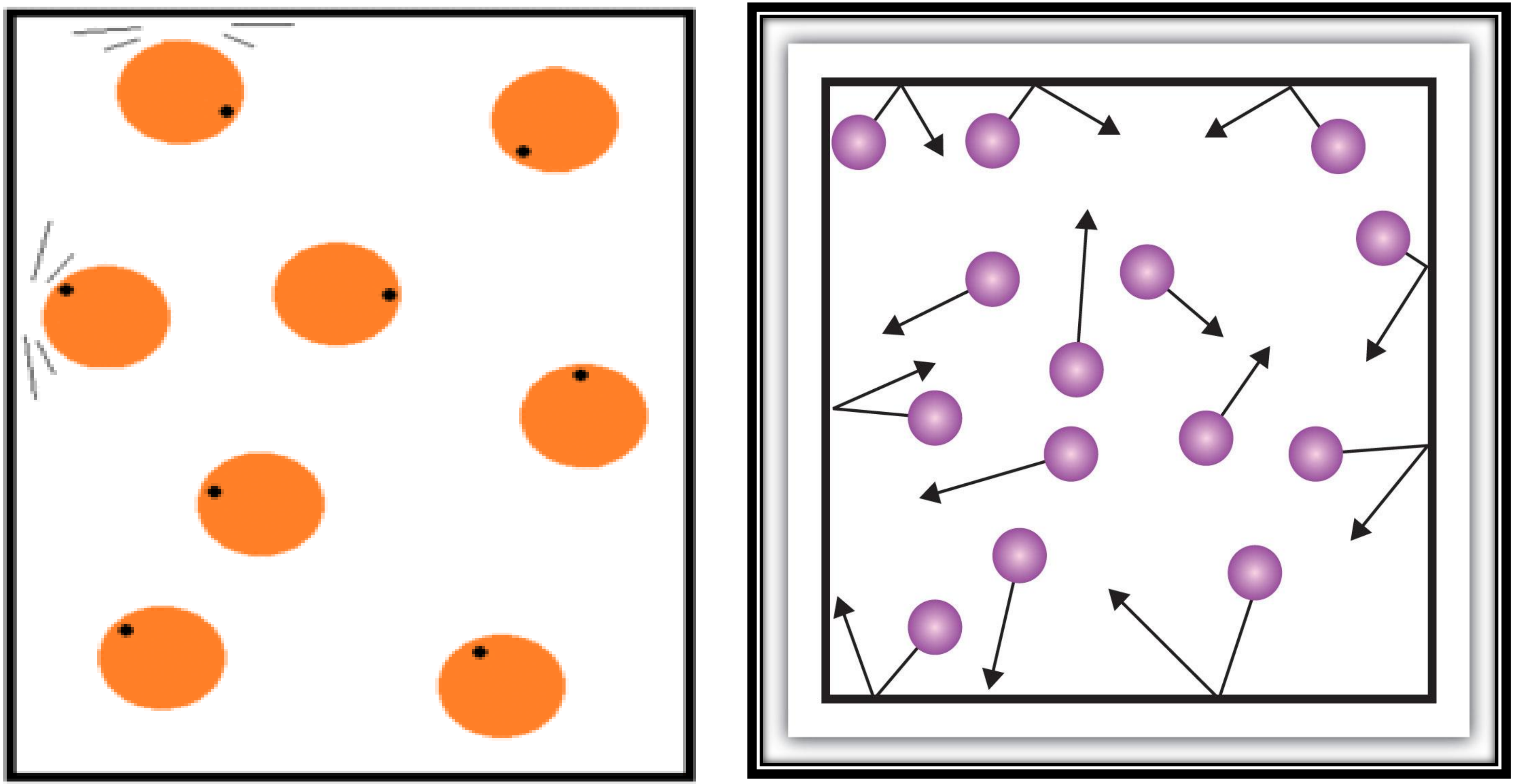
DIFFERENCE BETWEEN IDEAL GAS AND REAL GAS

Ideal gas	Real gas
Obeys all gas laws under all condition of temperature and pressure	Obeys gas lows only at low pressure and high temperature
Volume occupied by ideal gas is negligible as compare to total volume	Volume occupied by real gas is not negligible
No intermolecular force of attraction between ideal gas molecules	There are Intermolecular force of attraction between real gas molecules
Collisions between ideal gas molecule are elastic	Collisions between real gas molecule are non – elastic
Ideal gas obeys ideal gas equation	Real gas shows deviation from ideal gas equation

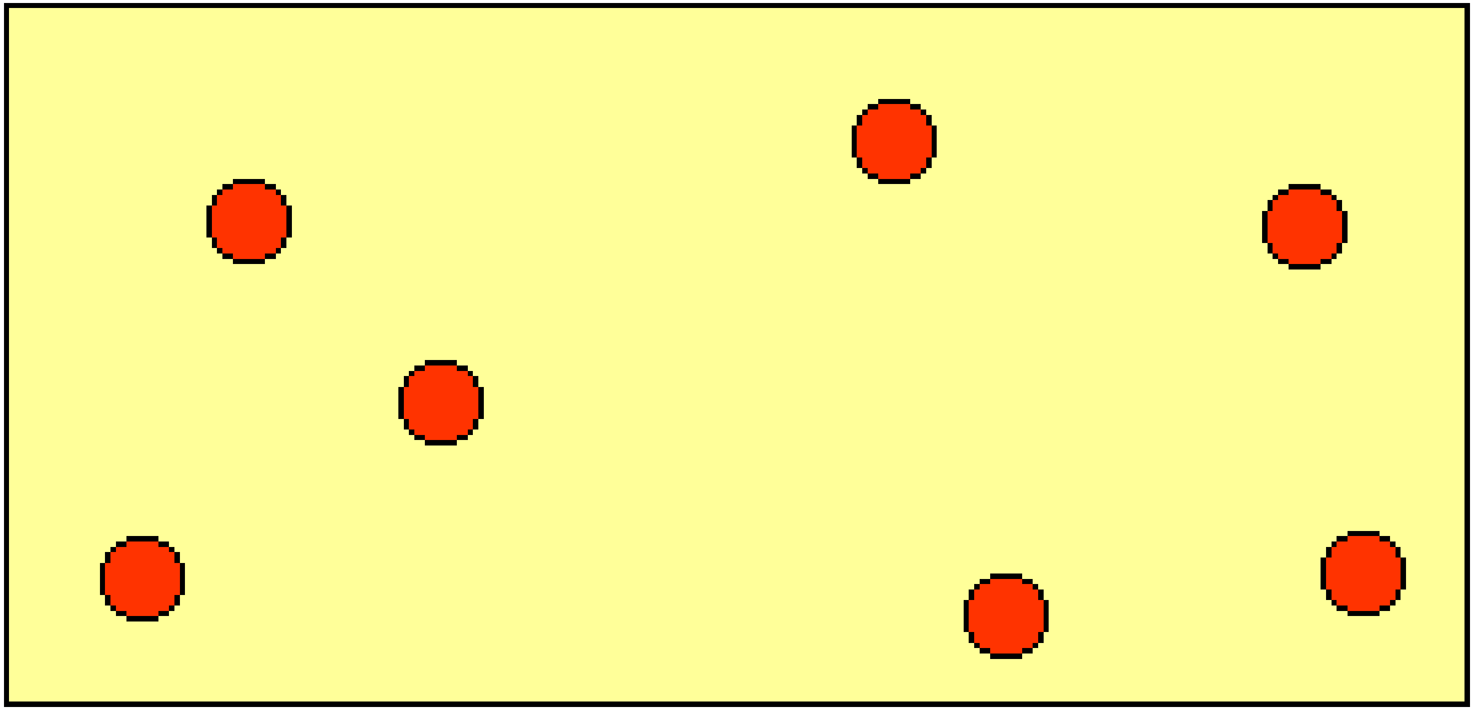
KINETIC MOLECULAR THEORY OF GAS



- Gases are made up of a large amount of particles .
- There is no attraction between gas particles.
- Gases are spread very far apart.



- Particles are in constant random motion and move in straight lines until they collide with another body.



- Collisions between molecules are perfectly elastic.
- Collisions between particles do not affect net loss of kinetic energy.

LIQUEFACTION OF GAS

1869

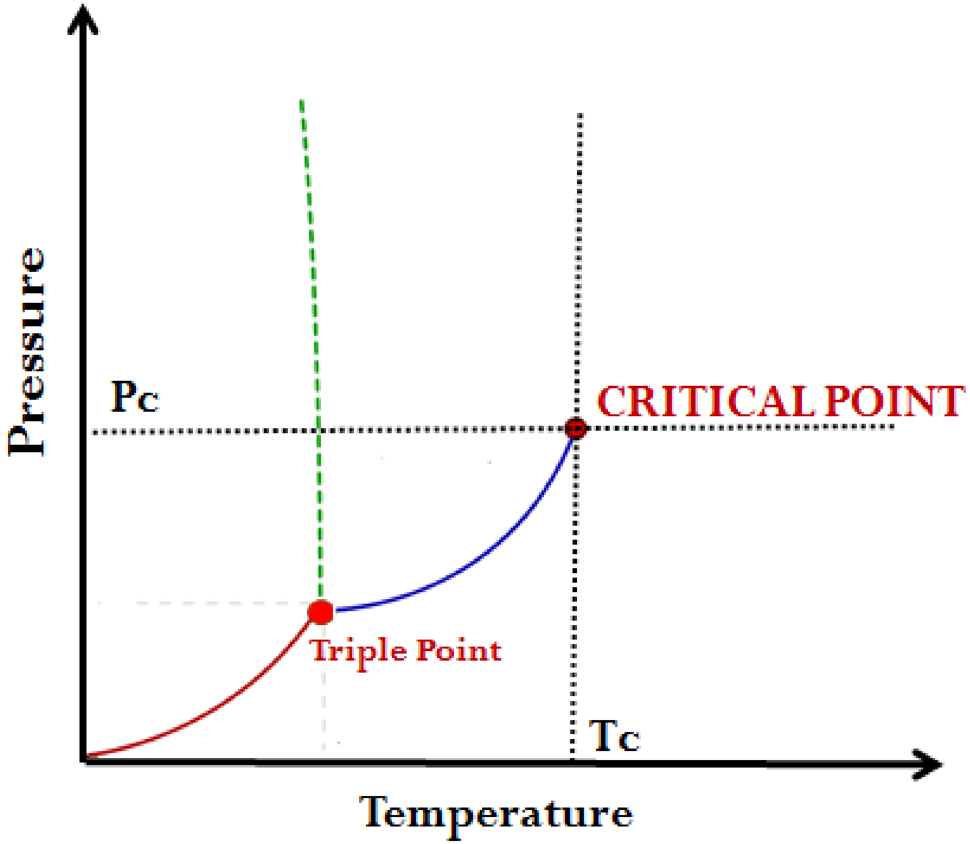
Thomas Andrew

variation in temperature and pressure

increase in pressure brings gas molecule close

Decrease in temperature removes energy

Liquefaction of gasses



- The physical conversion process by which gaseous state is converted to the liquid state is called as Liquefaction of gases.
- At critical temperature and critical pressure any gas behaves similar to its liquid and is said to be in critical state.
- Thomas Andrew concluded that all gasses below critical temperature can be liquefied by increasing pressure.
- This phenomenon is called as critical phenomenon and …

  Critical temperature (Tc, the temperature above which gas cannot be liquefied),

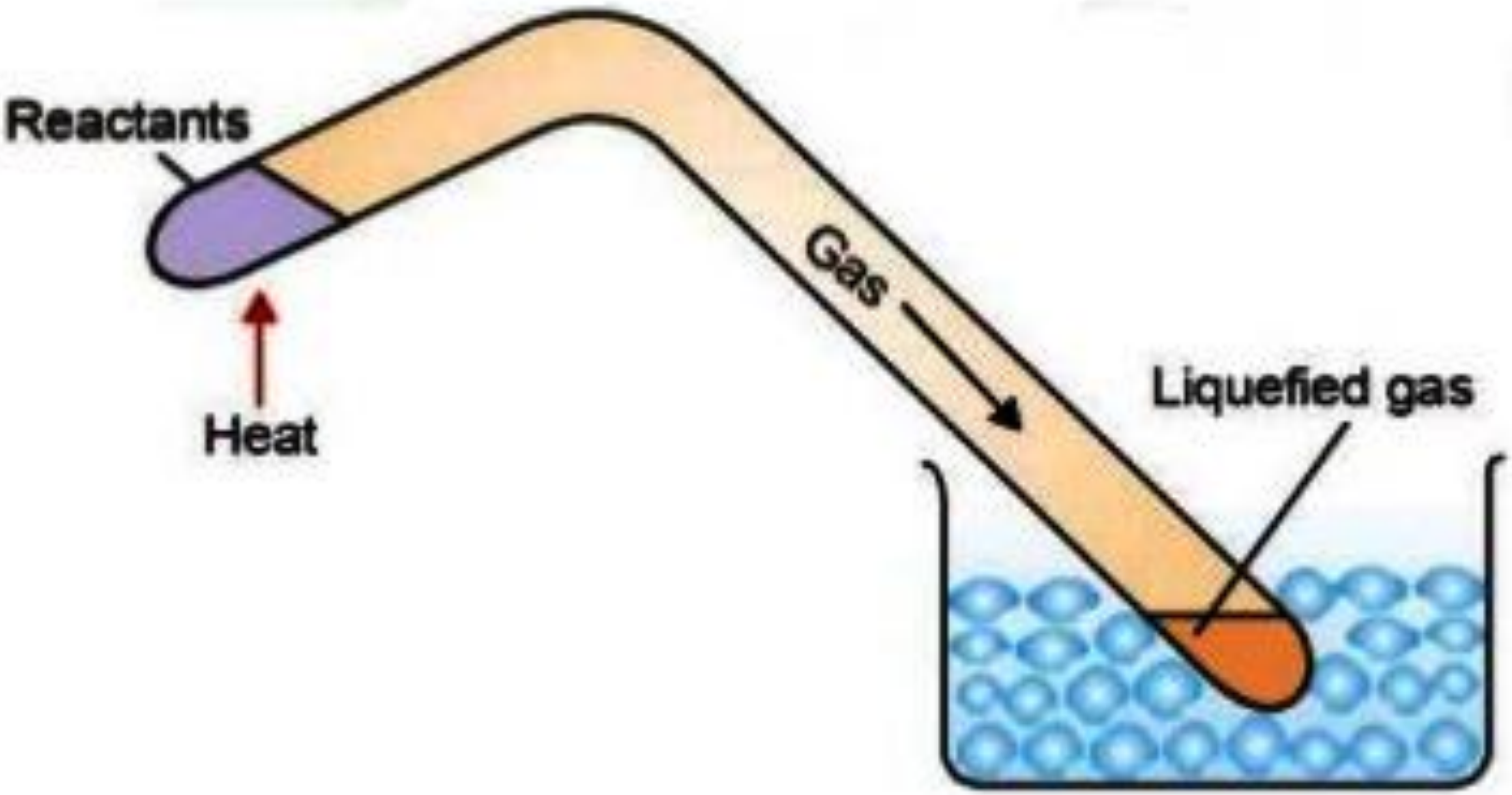
  Critical pressure (Pc, minimum pressure required to liquefy gas at critical temperature)

  Critical volume (Vc, volume occupied by one mole of gas at critical temperature and critical pressure)
- Tc, Pc and Vc are called as critical constants.

METHOD for LIQUEFACTION of GAS

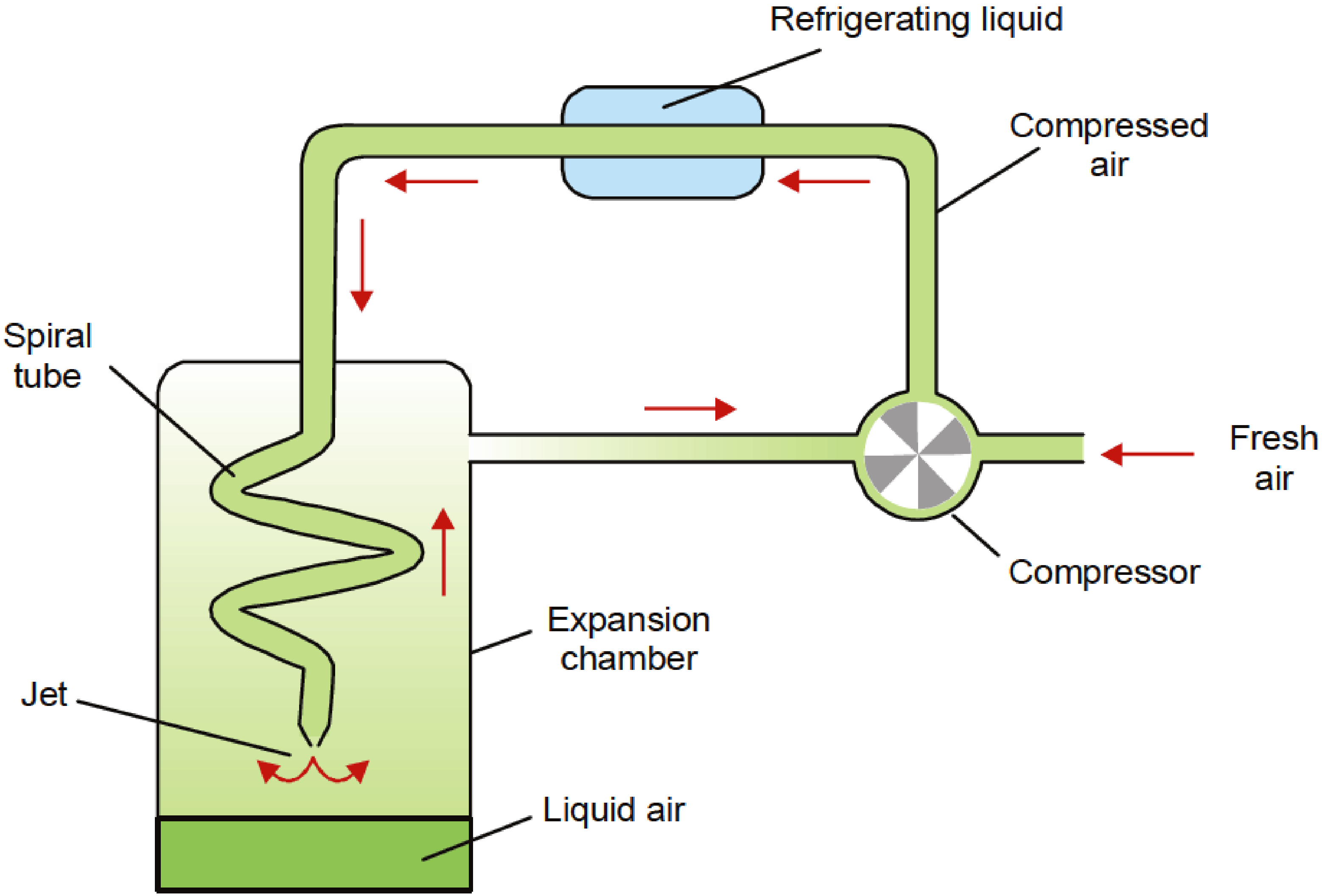
- **Faraday’s Method**
- **Linde’s Method**
- **Cloude’s Method**

FARADAY's METHOD



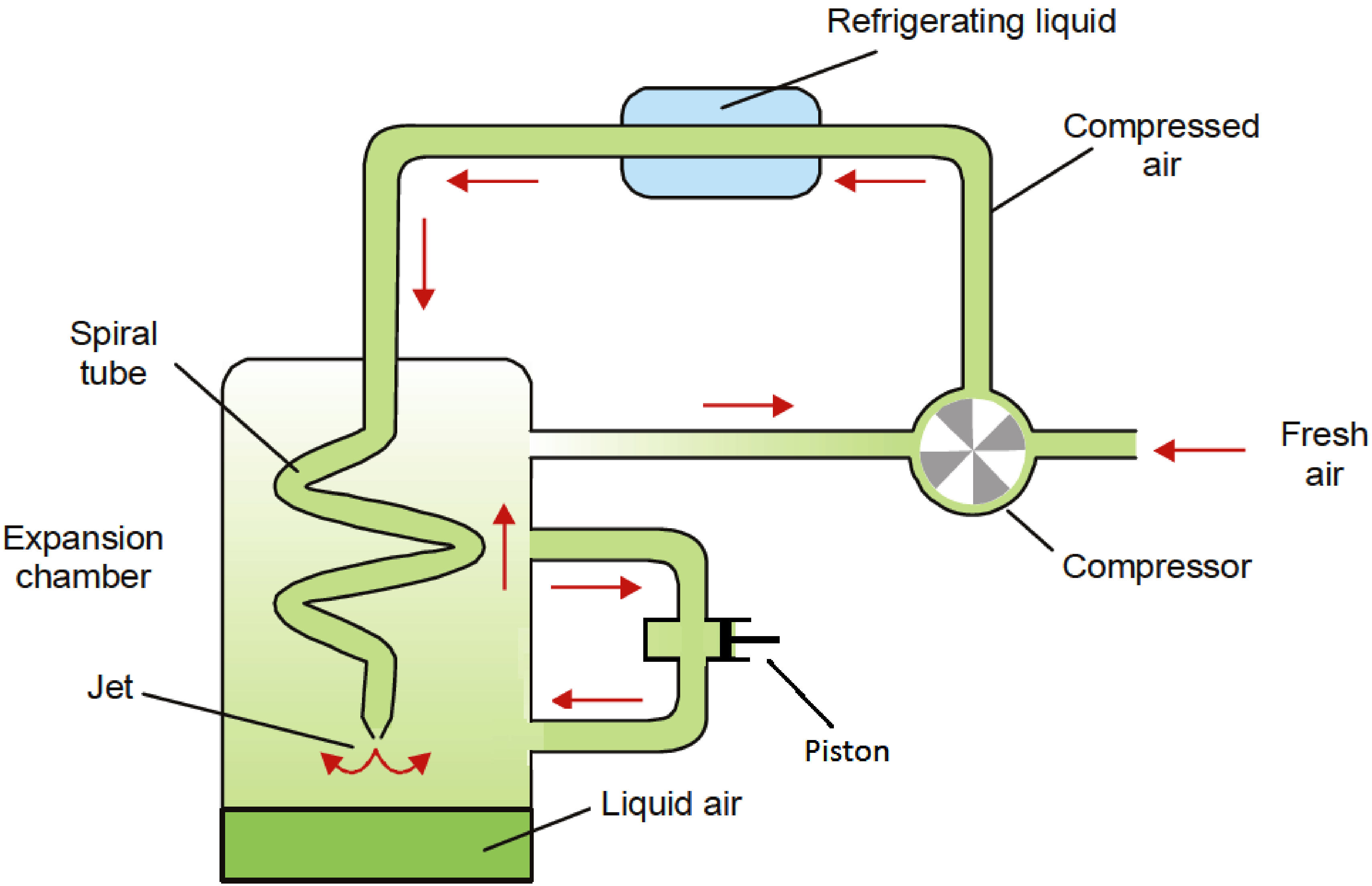
- **1823 – Michael Faraday**
- **Principle:** The Faraday method is based upon the principle of cooling of gas by freezing mixture where gas loses some of its kinetic energy in form of heat and velocity of molecule decreases.
- Faraday was able to liquefy gases with critical temperature just above or below atmospheric temperature.
- For external cooling of gas Faraday used freezing mixture of ice with various salts.
- The amount of heat is used to melt the ice and to dissolve the salt. Both melting of ice and dissolution of salt are the endothermic processes resulting into lowering of temperature below critical temperature.
- Cooling of gas below critical temperature with subsequent condensation results in removal of heat of vaporization thus accomplishing Liquefaction of gas.

LINDE's METHOD



- **1895 – Carl von Linde**
- **Principle:** The Linde's Method is based upon the principle of Joule-Thomson effect which states that when a gas is allowed to expand adiabatically from a region of high pressure to a region of extremely low pressure, it is accompanied by cooling.
- Linde used an apparatus where dry air compressed at 200 atmosphere followed by refrigeration using refrigerating liquid like ammonia resulting into removal of heat of compression.
- The compressed gas is passed through a copper coil to an expansion nozzle within a Dewar flask
- The expansion of air at the jet results into considerable drop of temperature. By repeating the process of compression and expansion the temperature of dry air reaches to critical temperature low enough to liquefy.

CLOUDE's METHOD



- **1902 – Georges Claude**
- **Principle:** The Cloude's method is based upon the principle that when a gas expands adiabatically against an external pressure (as a piston in an engine), it does some external work. Since work is done by the molecules at the cost of their kinetic energy, the temperature of the gas falls causing cooling.
- Cloude used an apparatus where Air is compressed to about 200 atmospheres and is passed through the pipe.
- A part of the air goes down the spiral towards the jet nozzle and a part of the air is led into the cylinder provided with an air tight piston.
- Here the air moves the piston outwards and expands in volume as a result of which considerable cooling is produced.

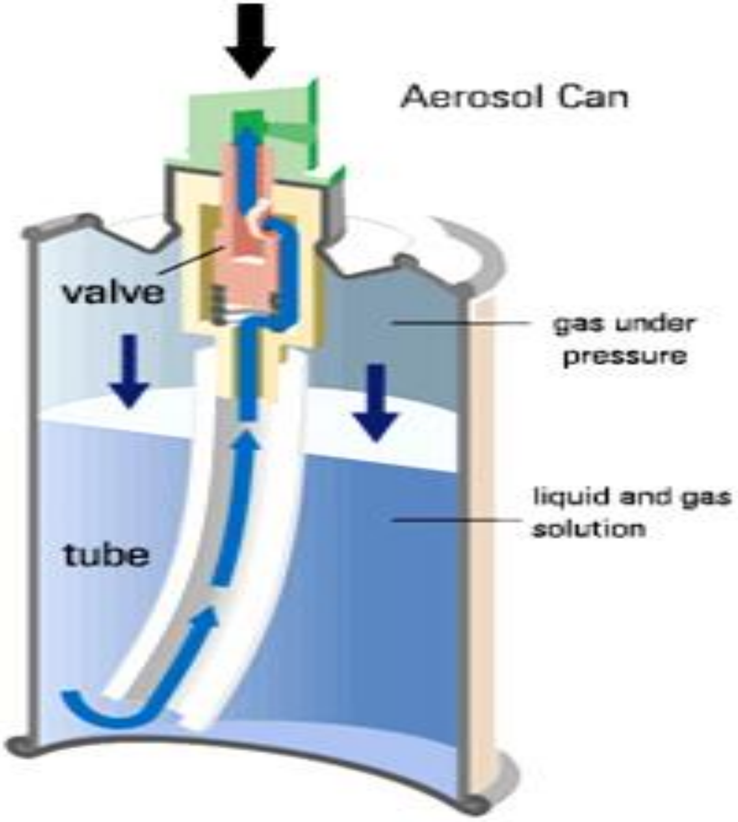
- The cooled air passes up the liquefying chamber during which process it cools the portion of the incoming compressed air.
- The precooled incoming compressed air then experiences Joule-Thomson expansion when passed through Jet nozzle and gets cooled further.
- The above process takes place repeatedly till the air is liquefied.
- The basic difference between Linde’s Method and Cloude’s Method is here in Cloude’s Method the gas is allowed to perform mechanical work as a added task along with overcoming intermolecular forces.

AEROSOL

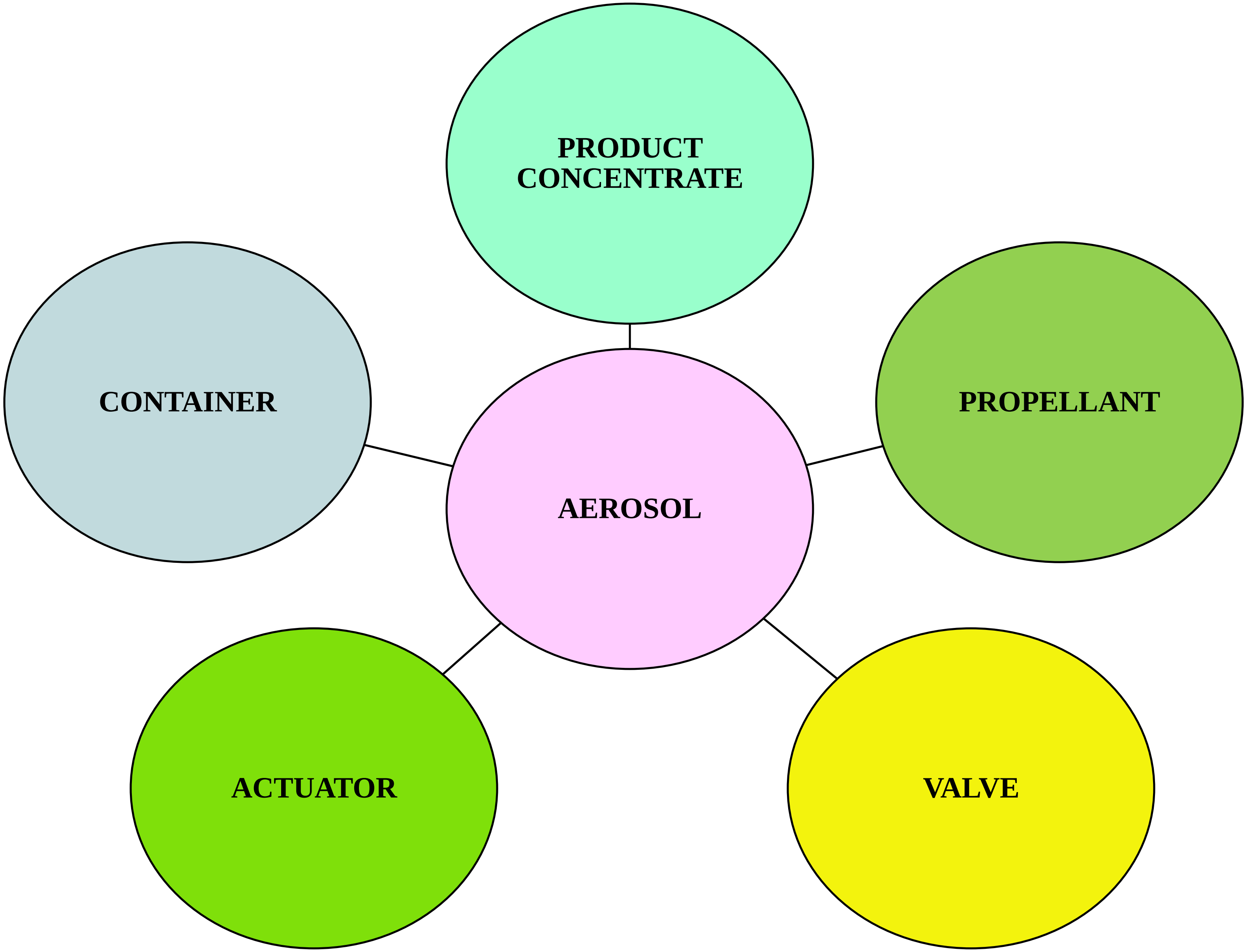
- In1941 aerosol spray was first introduced by Americans Lyle Goodhue and William Sullivan.
- In 1950 Ricker Laboratories introduced pressurized aerosol
- Liquefied gas with power to expel content.
- Suspension of fine solid particles or liquid droplets in air or gas.
- Can be natural or anthropogenic

DEFINITION (AEROSOL)

- Aerosol is the system that depends on power of compressed or liquefied gas to expel the content from container.



COMPONENTS



PRODUCT CONCENTRATE

CONTAINER

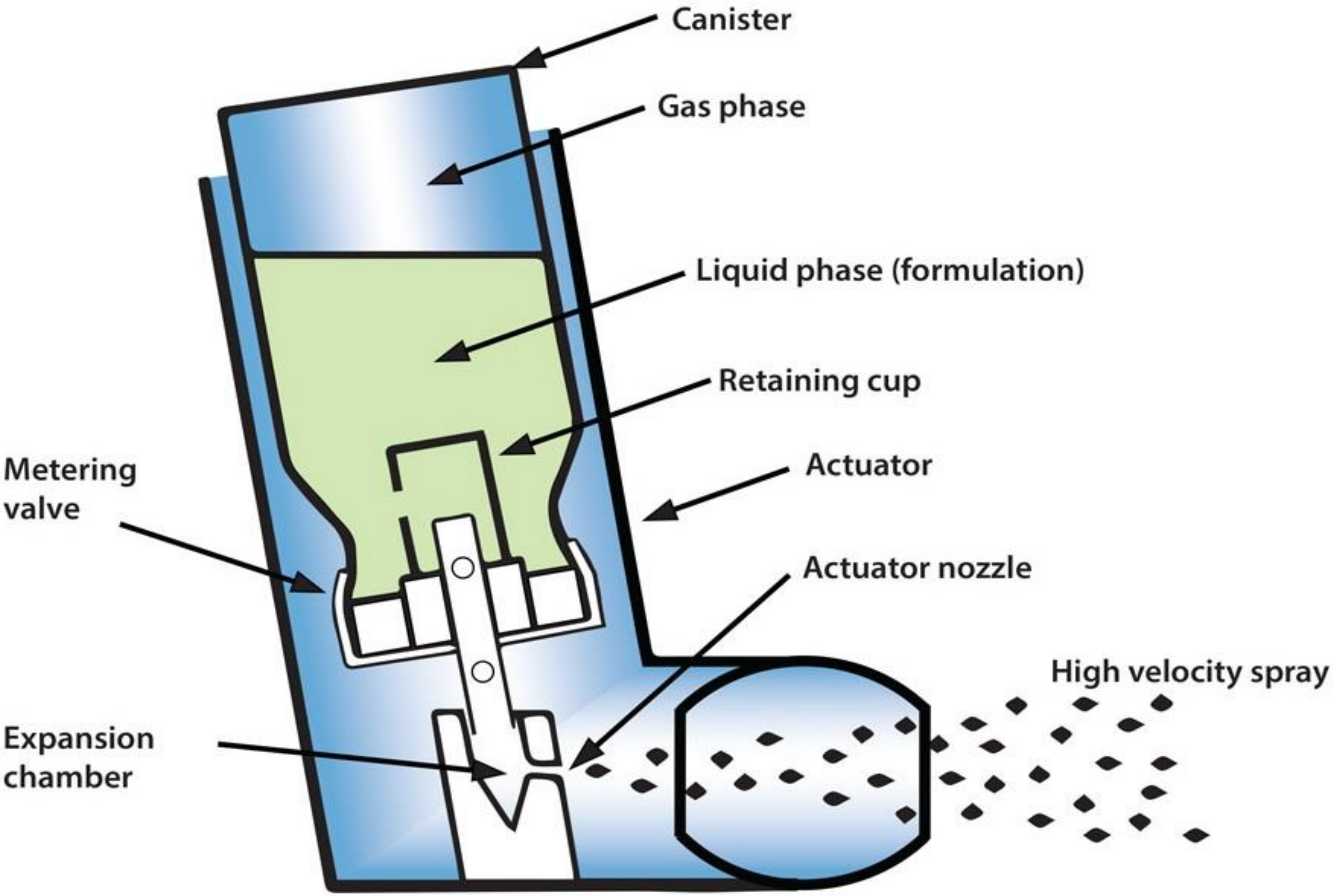
PROPELLANT

AEROSOL

ACTUATOR

VALVE

COMPONENTS


Canister
Gas phase
Liquid phase (formulation)
Retaining cup
Actuator
Metering valve
Actuator nozzle
High velocity spray
Expansion chamber

Product Concentrate

- Mixture of one or more active ingredients and other necessary agents like solvent, antioxidant and surfactant.
- The choice of solvent is based on the type either as solution. suspension or emulsion.

continued…

SOLUTION

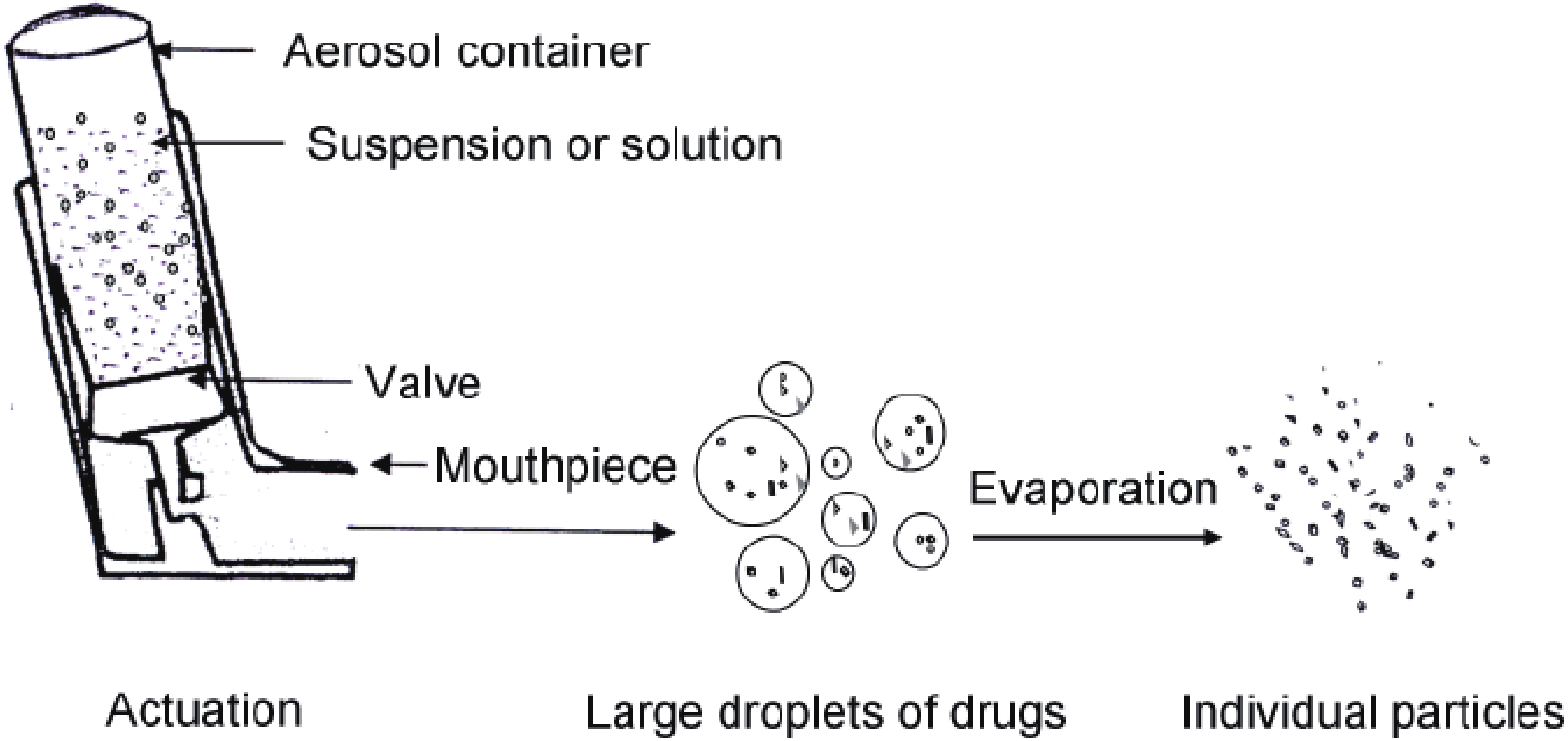
continued…

SOLUTION

- Active Ingredients like local anesthetics, anti-inflammatory, anti asthmatics etc are used in solution
- Solvents may also be added to the formulation to retard the evaporation of the propellant e.g. ethyl alcohol, propylene glycol, ethyl acetate etc
- The particle sizes of the sprays can vary from 5 to 10µm in inhalation aerosols and 50 to 100 µm for topical sprays.
- They contain 50 to 90% propellant for topical aerosols and up to 99.5% propellant for oral and nasal aerosols.
- As the percentage of propellant increases, so does the degree of dispersion and the finest of the spray.
- As the percentage of propellant decreases, the wetness of the spray will increase.

continued…

SUSPENSION



continued…

SUSPENSION

- Anti-asthmatic drugs, steroids, and antibiotics are delivered as suspension aerosols.
- Suspensions aerosols can be made when the product concentrate is insoluble in the propellant or mixture of propellant and solvent, or when a co-solvent is not desirable.
- When the valve is actuated, the suspension formulation is emitted as an aerosol and the propellant rapidly vaporizes and leaves a fine dispersion of the product concentrate.
- Formulation considerations for suspension aerosols, include agglomeration, particle size growth, valve clogging, moisture content, and particle size of the dispersed aerosolized particles.
- Lubricants such as isopropyl myristate and light mineral oil, and surfactants such as sorbitan trioleate, oleic acid, and lecithin have been used to overcome the difficulties of particle size agglomeration and growth which are directly related to the clogging problems.
- The moisture content of the entire formulation should be kept below 200 to 300 ppm so all of the ingredients need to be the anhydrous form of the chemical or be capable of becoming anhydrous after a drying process.
- The particle size of the insoluble product concentrate ingredients should be in the 1 to 10 µm range for inhalation aerosols and between 40 to 50 µm for topical aerosols.

continued…

EMULSION

EMULSION

continued…

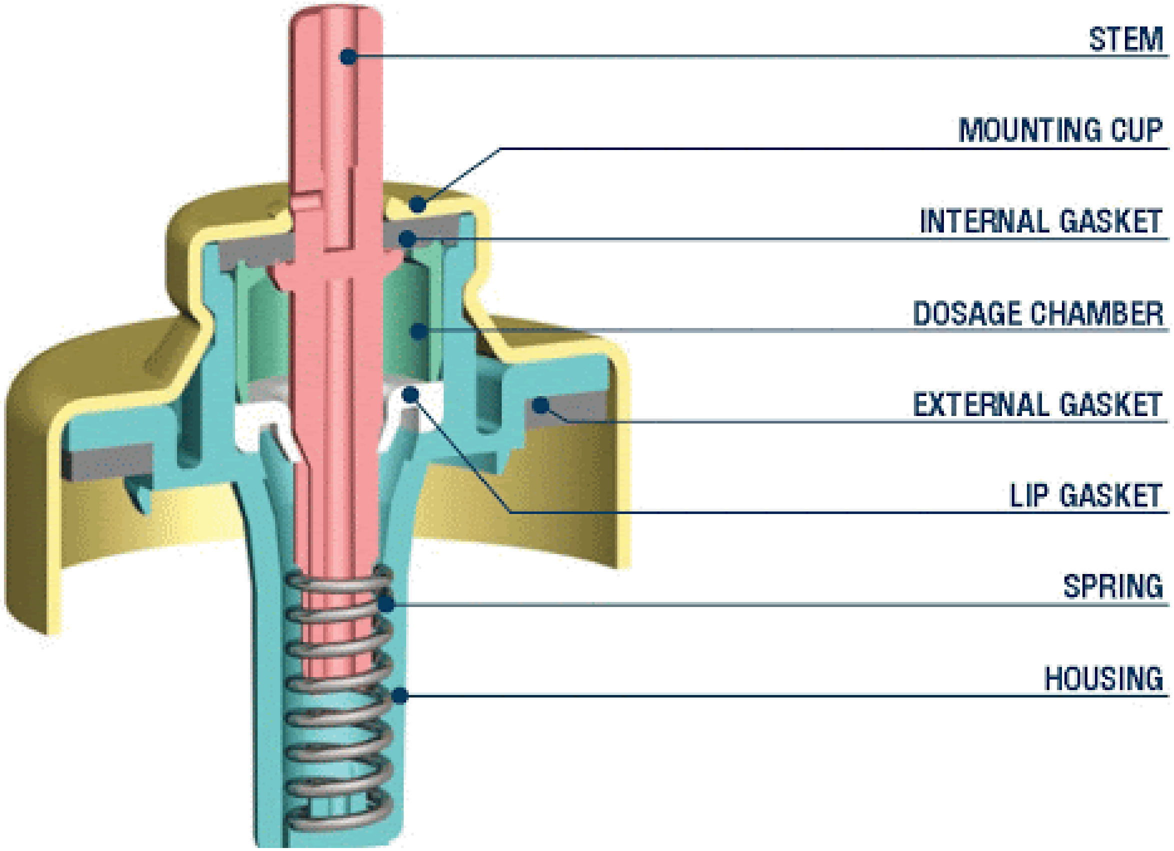
- The product concentrate in an emulsion aerosol will consist of the active ingredient, aqueous and/or nonaqueous vehicles, and a surfactant.
- Depending on the components, the emitted product can be a stable foam (shaving cream type) or a quick breaking foam.
- Foams are produced when the product concentrate is dispersed throughout the propellant and the propellant is in the internal phase; i.e., the emulsion behaves like o/w emulsions. When the propellant is in the external phase (i.e., like a w/o emulsion), foams are not created but sprays or wet streams result.
- Surfactants concentrate at the interface between the propellant and the aqueous phase forming a thin film referred to as the "lamella.“
- Surfactants used in emulsion aerosols have included fatty acids saponified with triethanolamine, anionic surfactants, and nonionic surfactants such as alkanolamides. The nonionic surfactants are present fewer compatibility problems because they charge no electronic charge.

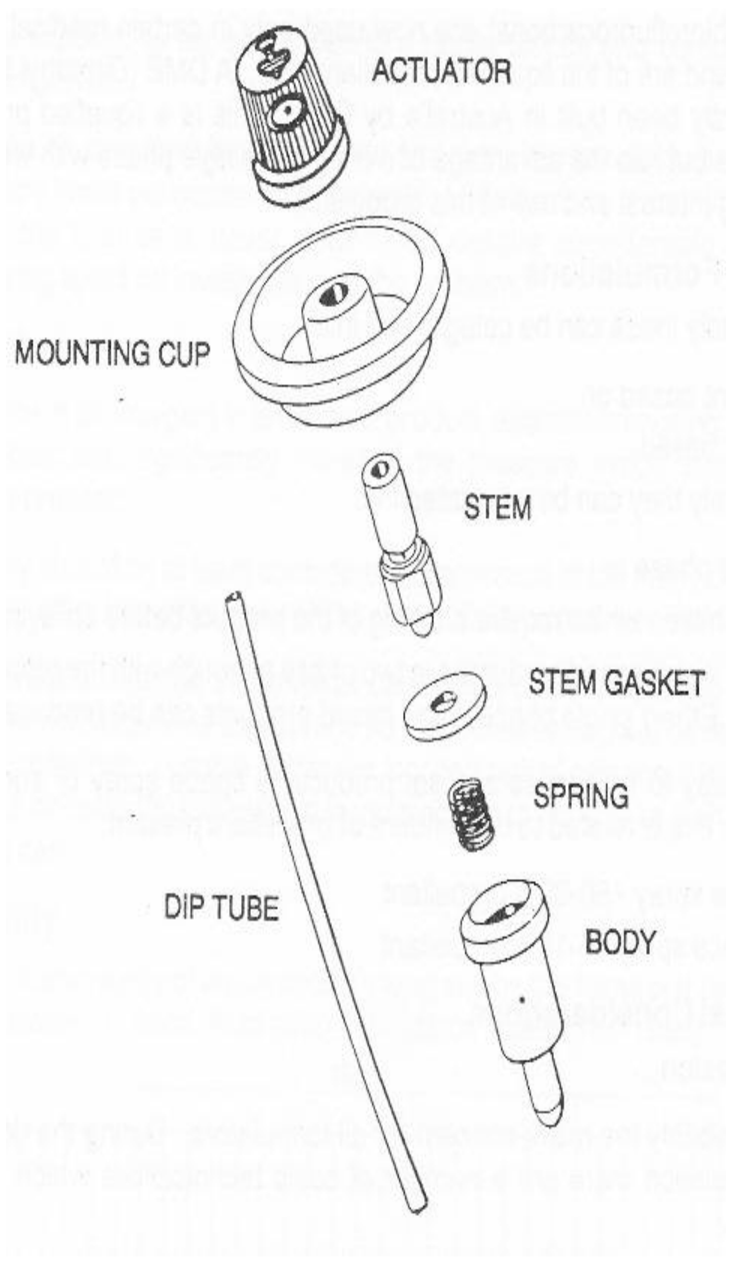
PROPELLANT

- The propellant provides the force that expels the product concentrate from the container and additionally is responsible for the delivery of the formulation in the proper form (i.e., spray, foam, semisolid).
- When the propellant is a liquefied gas or a mixture of liquefied gases, it can also serve as the solvent or vehicle for the product concentrate.
- A propellant is a chemical with a vapor pressure greater than atmospheric pressure at 40°C (105°F).
- The propellant having vapor pressure greater than atmospheric pressure develops required pressure in the container to expel the product concentrate in the desired form viz., spray, mist, solid, foam, stream etc.
- Types of propellants commonly used in pharmaceutical aerosols include chlorofluorocarbons, hydrocarbons, hydrofluorocarbons, hydrochlorofluorocarbons and, and compressed gases.

VALVE

- Valve are capable to deliver the content in desired form such as spray, foam, mist etc
- Basically there are two types of valves namely continuous spray valve and metering valve





The basic component of valve are

-**Ferrule (mounting cup)** : for attachment of valve to container

-**Housing** : The cylinder which which hold the spring and connects dip tube

-**Stem:** is the connection between actuator and spring

-**Gasket:** The key to aerosol can keeping the can airtight.

-**Spring:** Maintain pressure on gasket

-**Housing:** The cylinder which hold the spring and connects dip tube

-**Dip tube:** The hollow tube extends from valve to the bottom of container allowing the product to be pushed out through valve

ACTUATOR

- The actuator is the part of the can that dispenses the product.
- There are different types of actuators that are used for different product consistencies.

- The actuator controls the fineness of the product spray, as well as the amount of product that is dispensed.
- When you press down on it, the valve is opened. When the valve opens, the pressure is released from the top of the aerosol can and the pressurized propellant tries to escape from the can.
- However, the product filled bag prevents the propellant from escaping, so instead, the propellant pushes on the bag and forces the product out of the actuator.

CONTAINER

- They must be able to withstand pressure as high as 140-180 psig (pounds per sq inch gauge) at 130°F
- The selection of the container for a particular aerosol product is based on its adaptability to production methods, compatibility with the formulation, ability to sustain the pressure necessary for the product, the design and aesthetic appeal, and the cost.
- Aerosol containers are generally made of glass, metals (e.g., tin plated steel, aluminum, and stainless steel), and plastics.

- Apart from design creativity chemical compatibility with the formulation compared to metal containers makes glass material preferable choice and the same material is not subject to corrosion.
- Preferentially glass containers used for the propellant producing pressure below 25 psig to provide the maximum pressure safety and impact resistance
- To increase the resistance to breakage, plastic coatings are commonly applied to the outer surface of glass containers.
- These plastic coatings serve many purposes:

1) prevent the glass from shattering into fragments if broken;
2) absorb shock from the crimping operation during production thus decreasing the danger of breakage around the neck;
3) protect the contents from ultraviolet light;
4) act as a means of identification since the coatings are available in various colors.

- Stainless steel is used when the container must be chemically resistant to the product concentrate. The main limitation of these containers is their high cost.
- Plastic containers have had limited success because of their inherent permeability problems to the vapor phase inside the container. Also, some drug-plastic interactions have limited the efficacy of the product.
- Tin-plated steel containers are light weight and relatively inexpensive. When required, special protective coatings are applied to the tin sheets prior to fabrication so that the inside of the container will be protected from corrosion and interaction between the tin and the formulation. The coating usually is an oleoresin, phenolic, vinyl, or epoxy coating.

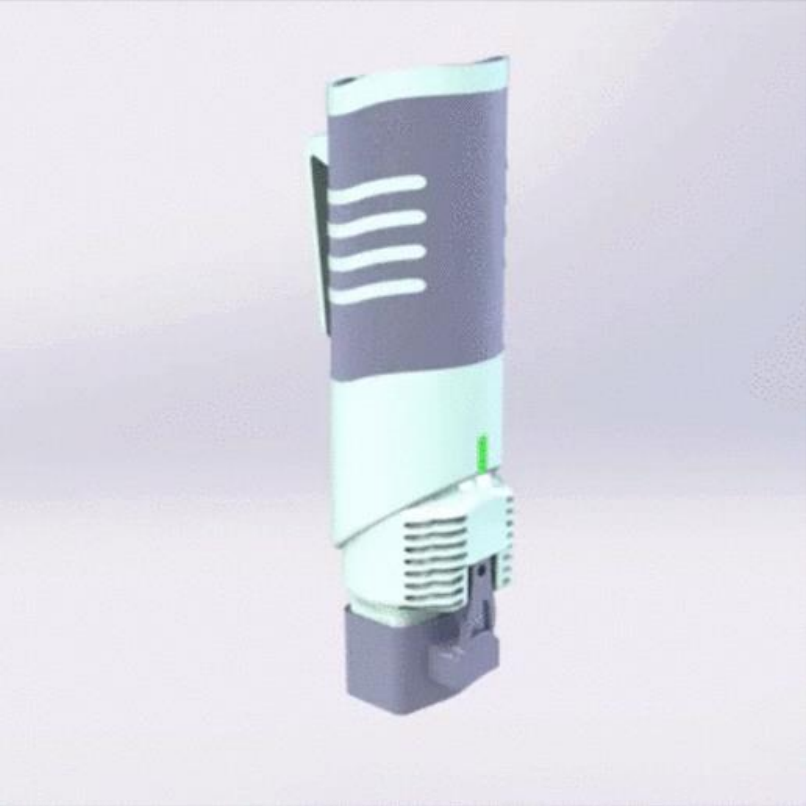
- Aluminum is used in most MDIs and many topical aerosols. This material is extremely light weight and is less reactive than other metals. Aluminum containers can coated with epoxy, vinyl, or phenolic resins to decrease the interaction between the aluminum and the formulation. The aluminum can also be anodized to form a stable coating of aluminum oxide. Most aluminum containers are manufactured by an impact extrusion process that make them seamless. Therefore, they have a greater safety against leakage, incompatibility, and corrosion.

Pressure Limitations of Aerosol Containers

Container Material	**Maximum Pressure (psig)**	**Temperature (^{o}F)**
Tin-plated steel	180	130
Uncoated glass	< 18	70
Coated glass	< 25	70
Aluminum	180	130
Stainless Steel	180	130
Plastic	< 25	70

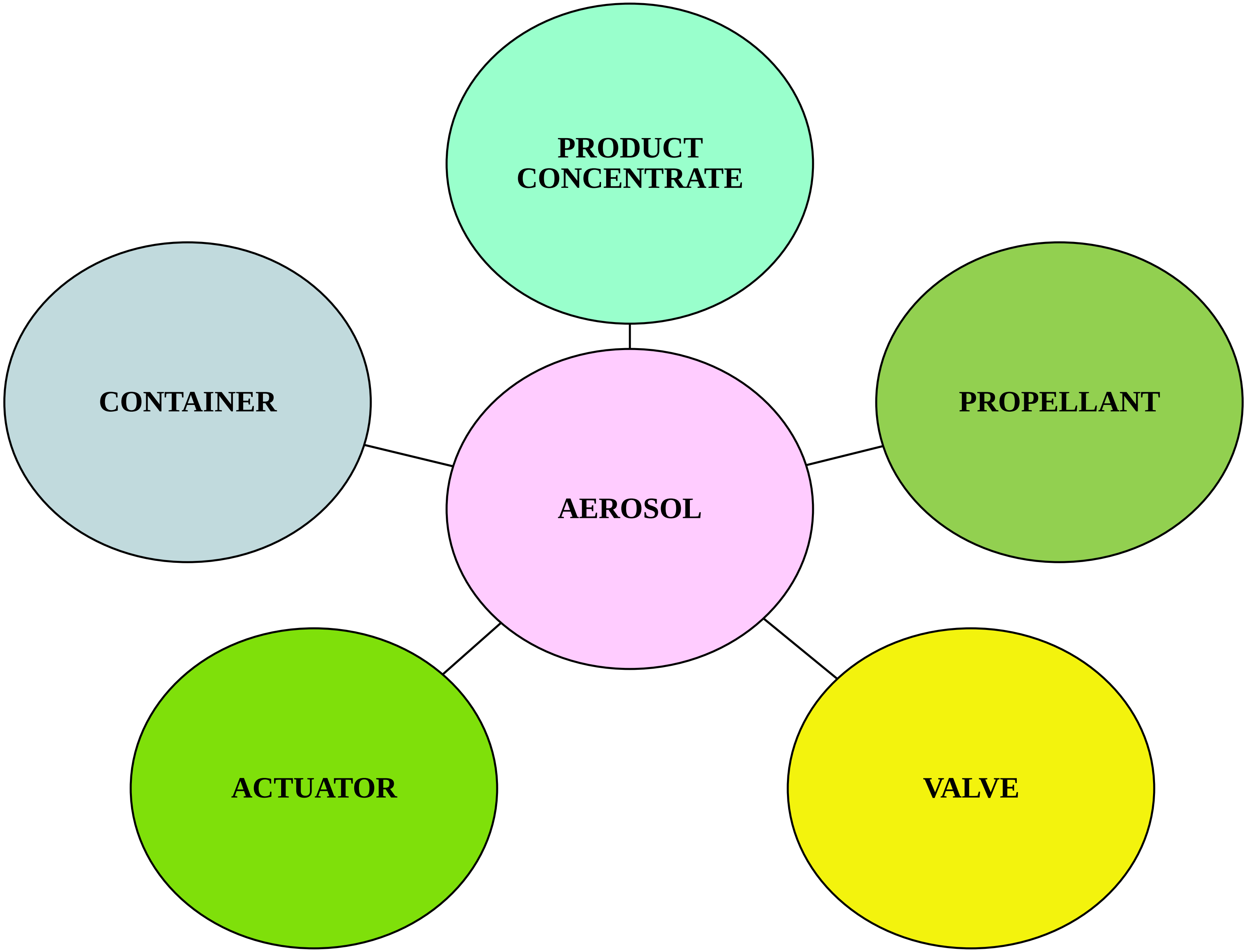
DEFINITION (INHALER)

Inhalers are the aerosols formulated in the manner to inhale through the mouth and into the respiratory tract for local or systemic delivery.



- Polydisperse System - meaning that they contain particles of different sizes.
- Monodisperse System - that consist of particles of a single size
- The optimum aerodynamic particle size distribution for most inhalation aerosols has generally been recognized as being in the range of 1-5 μm.

COMPONENTS



PRODUCT CONCENTRATE

CONTAINER

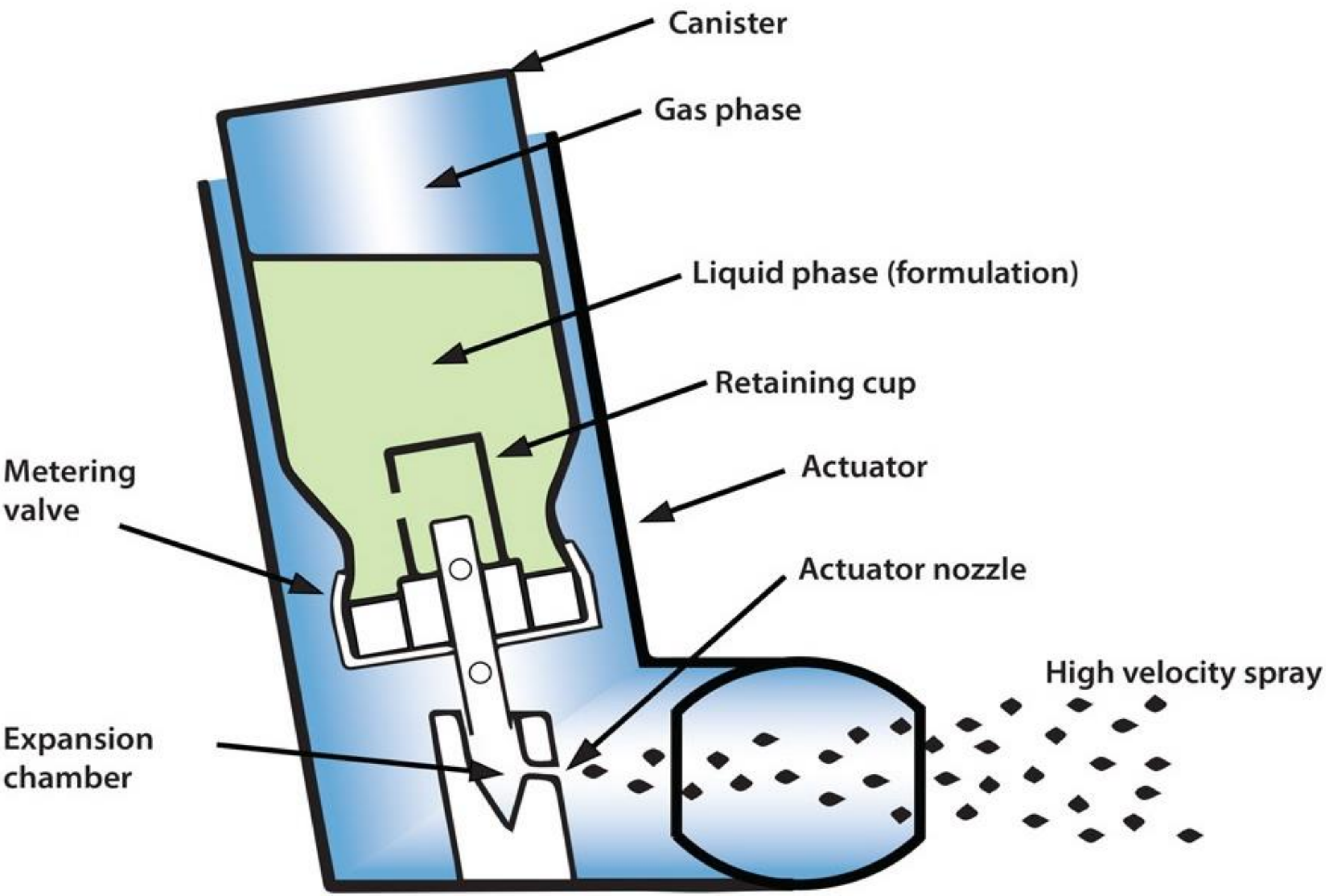
PROPELLANT

AEROSOL

ACTUATOR

VALVE

COMPONENTS


Canister
Gas phase
Liquid phase (formulation)
Retaining cup
Actuator
Metering valve
Actuator nozzle
High velocity spray
Expansion chamber

TYPES OF INHALERS

- There are three basic types of inhalers:
  - Metered dose inhaler (MDI)
  - Dry powder inhalers (DPI)
  - Soft mist inhalers (SMI)

METERED DOSE INHALER

- The MDI device consists of a canister, and actuator, and sometimes a spacer.
- The canister itself consists of a metering dose valve with an actuating stem.
- The formulation resides within the canister and is made up of the drug, a liquefied gas propellant, and often stabilizing excipients.
- Actuation of the device releases a single metered dose of liquid propellant that contains the medication.
- The volatile propellant breaks up into droplets which then evaporate, creating an aerosol containing micronized drug that is inhaled into the lungs.

DRY POWDER INHALER

- DPI device deliver a powder dosage form to the lungs. Most DPIs include an active ingredient and one or more excipient to aid powder dispersion and flow.
- There are two types of dry powder inhalers, passive or breath actuated devices, and active devices.
- With passive devices, the energy for dispersion is generated by the patient's inspiratory effort.
- In contrast, active devices minimize inspiratory effort by using an independent means (motor or compressed gas) to fluidize the powder. In the literature, the active devices have also been referred to the third generation DPI.

SOFT MIST INHALER

- A soft mist inhaler (SMI) is a newer type of inhaler that gives you a pre-measured amount of medicine in a slow-moving mist.
- It creates a cloud of medicine that you inhale without the help of a propellant. Because the mist contains more particles than MDIs and DPIs and the spray leaves the inhaler more slowly, more of the drug gets into your lungs.

HUMIDITY AND RH

- **Humidity** is a measure of the amount of (invisible) water vapor in the atmosphere.
- **Absolute humidity** indicates the actual amount of water vapor present in a sample of air.
- **Relative humidity** is the ratio of the actual mass of vapor in the air to the mass of vapor in saturated air at the same temperature.
- **Specific humidity** is the ratio between the amount of water vapor in air and the total mass of the mixture of air and water vapor.

INTRODUCTION

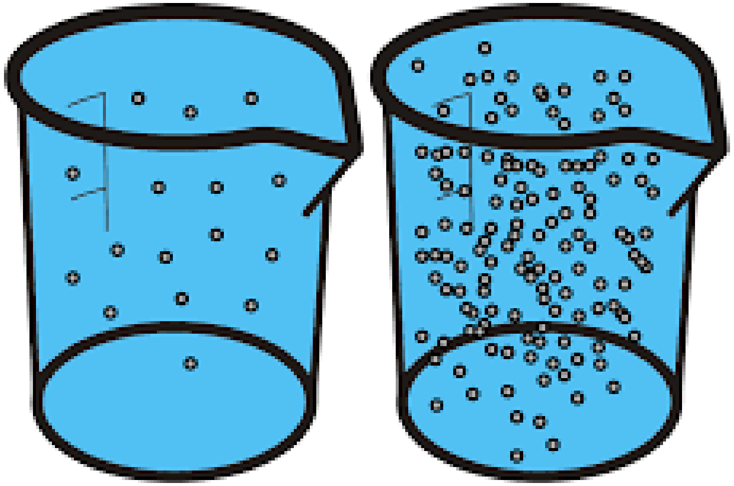
- Absolute humidity indicates the actual amount of water vapor present in a sample of air, or the vapor concentration, the mass of water vapor in a given quantity of air. 1 kg of air might hold up to 25 grams of water vapor in the tropics, but almost nothing in cold Polar Regions.
- Relative humidity is the ratio of the actual mass of vapor in the air to the mass of vapor in saturated air at the same temperature. For example, air at 10^0C contains 9.4 $g/m^3$of water vapor when saturated. If air at this temperature contains only 4.7 g/m^3 of water vapor, then the relative humidity is 50%.

RELATIVE HUMIDITY

Relative humidity is a way of describing how much humidity is present in the air, compared to how much there could be.

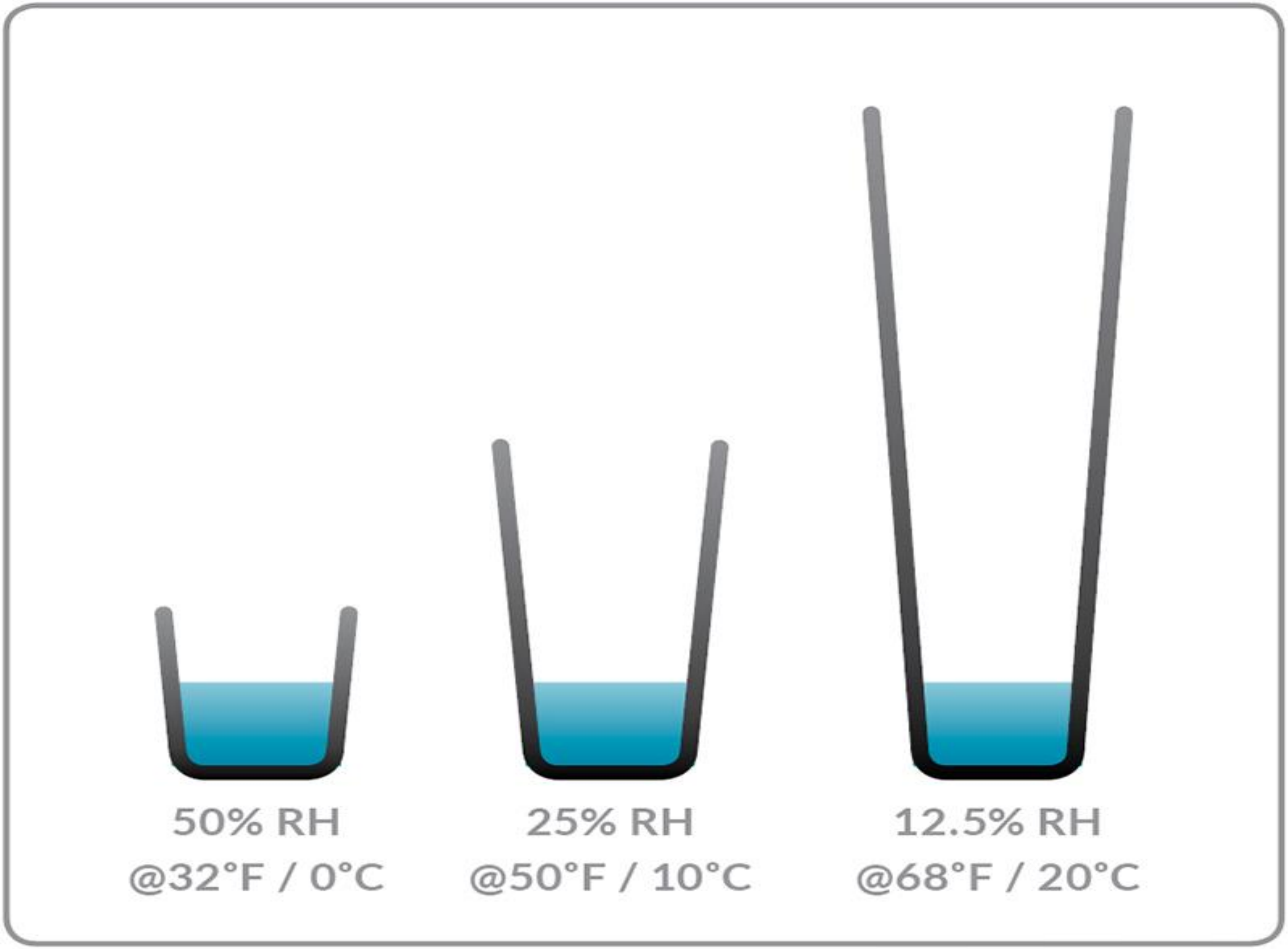
RH and VP

- The capacity of air to hold water vapor is based on vapor pressure of water.



- The capacity of air to hold water vapor is based on vapor pressure of water.
- The liquid and solid phases are continuously giving off vapor because some of the molecules have high enough speeds to enter the gas phase.
- The capacity of air to “hold” water vapor is determined by the vapor pressure of water and has nothing to do with the properties of air.
- A reading of 100 percent relative humidity means that the air is totally saturated with water vapor and cannot hold any more. When air can’t “hold” all the moisture, then it condenses as dew.

RH and TEMPERATURE



- As the air temperature changes, water holding capacity of air changes because the warmer the air is, the more moisture it can hold.
- In other words, as the temperature goes up, the volume of container (Vc) increases in size and can hold more moisture.
- For example, let’s assume that the container is half full (50% RH) at 32°F (0°C). If we raise the air temperature about 18°F to 50°F (10°C), the size of the container roughly doubles. But because the amount of water stays the same, RH drops by half from 50% to 25%. If we raise the temperature again to near room temperature (68°F/20°C), the size of the container roughly doubles again, and RH again drops by approximately half, from 25% to 12.5%. (This doubling in the container’s size for every 18°F increase in temperature is an approximation that serves as a “soft” rule of thumb between freezing and room temperature.)

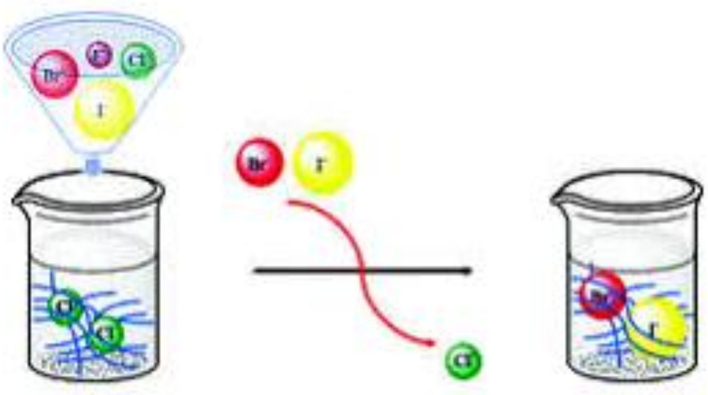
- Building scientists are particularly concerned, however, when warm inside air leaks out into the exterior walls of the building, where it encounters surfaces that are colder than the indoor temperature. The closer the moisture-laden indoor air gets to the outside layers of the building envelope, the colder those surfaces get. And at each step along the way, the size of the bucket gets smaller and smaller.

LIQUID COMPLEXES

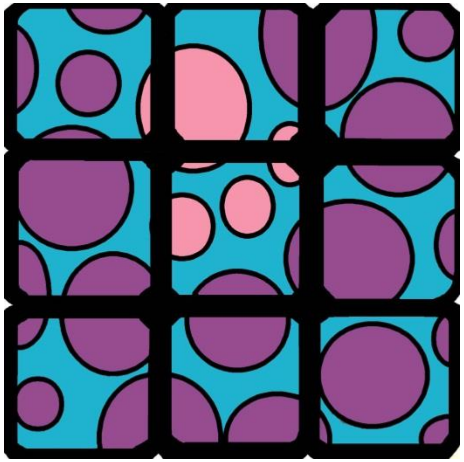
- Liquid Complexes are gases or liquids that contain particles of other substances dispersed within them.
- Liquid Complexes are materials intermediate between conventional liquids and solids, displaying fluid-like as well as solid-like behavior.

- Conventional solids and liquids are made up of atoms and molecules. Liquid Complexes are also made up of atoms and molecules at the very smallest scales. However, these atoms and molecules are organized to form larger structures, which in turn make up the bulk fluid.
- The observed behavior of these materials cannot be explained from the chemical constituents alone, without taking into account these intermediate scales of organization.

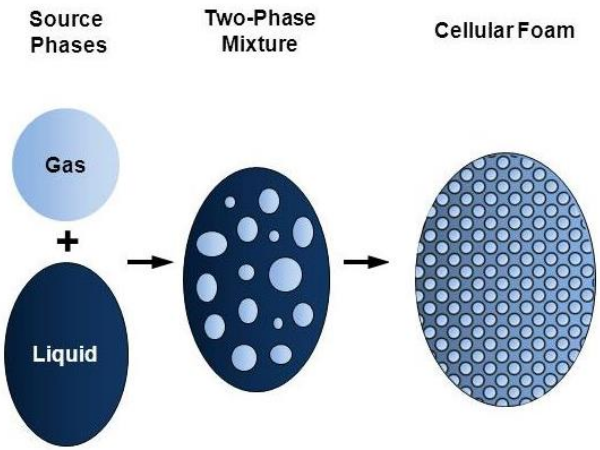
Solid-liquid (suspensions or solutions of macromolecules such as polymers), solid-gas (granular), liquid-gas (foams) and liquid-liquid (emulsions)



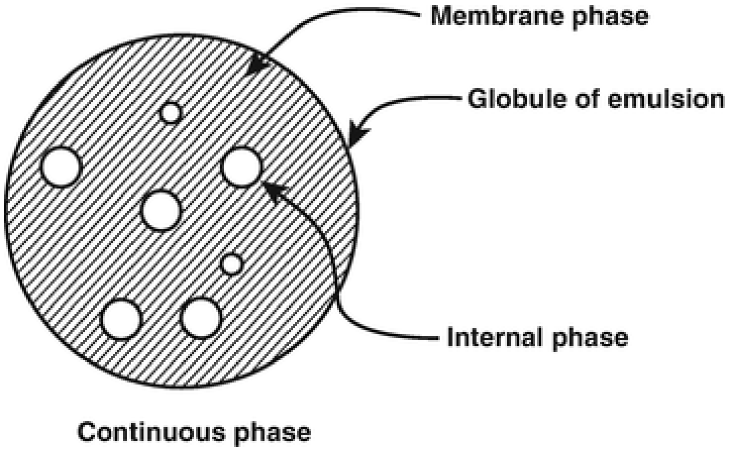
Solid-liquid



solid-gas (granular)



liquid-gas (foams)



liquid-liquid(emulsions)

PROPERTIES

- Many of these systems are inherently disordered and strongly heterogeneous with large fluctuations on a wide range of length and time scales.
- 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.

LIQUID CRYSTALS

- Liquid crystal is a state of matter that blends the structures and properties of the liquid and crystalline solid states.
- The liquid crystal state where the molecules are separated in parallel layers of quasi crystalline order lying is called as mesophase or (mesomorphic phases).

PROPERTY

- 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.
- A true liquid is isotropic (properties are uniform in all directions), Crystalline solids are anisotropic (properties vary with direction directions) but liquid crystal phase has many of the physical attributes of a liquid, but its molecular units are sufficiently ordered to give rise to some anisotropy.

PROPERTY

- The anisotropy of liquid crystals causes them to exhibit birefringence. That is, light that enters the crystal is broken up into two oppositely-polarized rays that travel at different velocities. Observation of a birefringent material between crossed polarizing filters reveals striking patterns and color effects.
- The molecule can slide one around the other, and layers can slide over one another. This molecular mobility generates fluidity in liquid crystal state.

PROPERTY

- Liquid crystal phases are generally cloudy in appearance, which means that they scatter light in much the same way as colloids such as milk. This light scattering is a consequence of fluctuating regions of non-uniformity as small groups of molecules form and disperses.
- Liquid crystals, like all other kinds of matter, are subject to thermal expansion. As the temperature rises, the average spacing between the aligned molecules of a phase increases.

PROPERTY

- Surface properties of a molecular model of a liquid crystal can be studied using a density functional theory. The intermolecular interaction includes all terms which break the orientational symmetry at the interface.

TYPES

- Depending on the arrangement of the molecules or its symmetry, liquid crystals are subdivided into four main types, or what is scientifically known as mesophases.

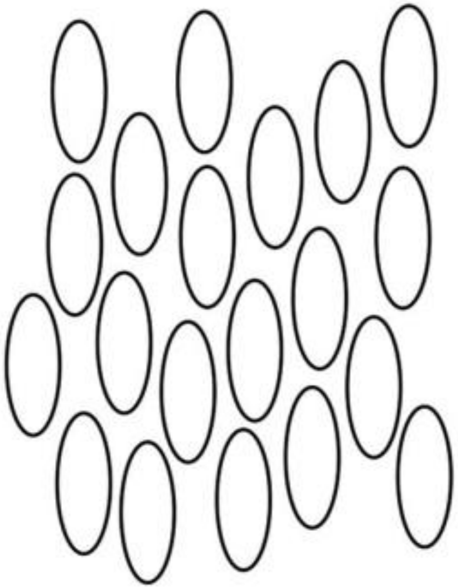
  - Nematics

  - Cholesterics

  - Smectics

  - Columnar

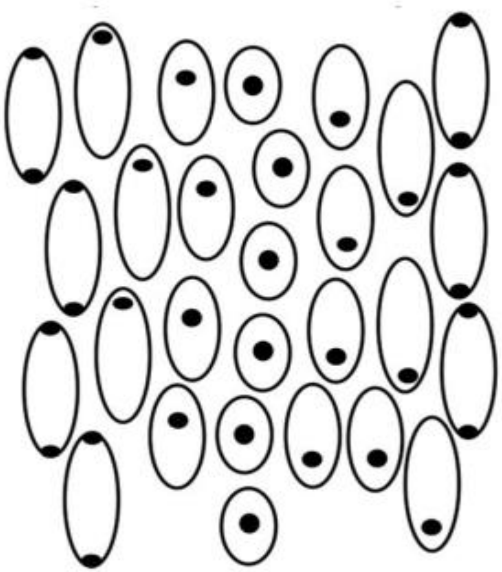
TYPES



nematic

- **Nematics:** The nematic phase is the simplest form of liquid crystal and is the phase in which the crystal molecules have no orderly position and are free to move any which way. However, while they have no specific order, during this phase the molecules do tend to point in the same direction.

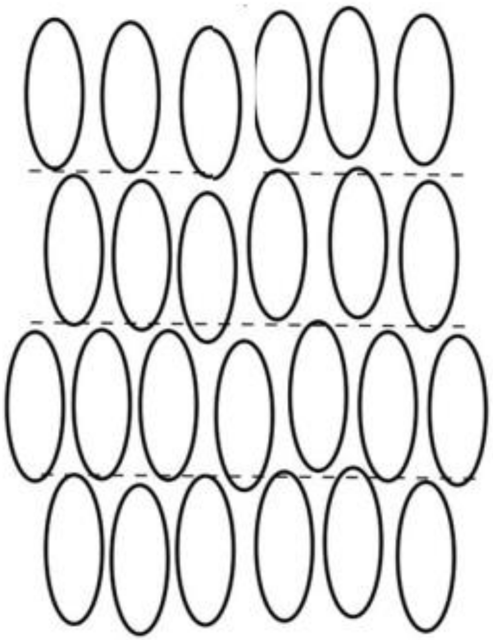
TYPES



cholesteric

- **Cholesterics:** The cholesteric phase, also known as chiral nematic phase, is characterized by the molecules being aligned and at a slight angle to one another, stacked within very thin layers.

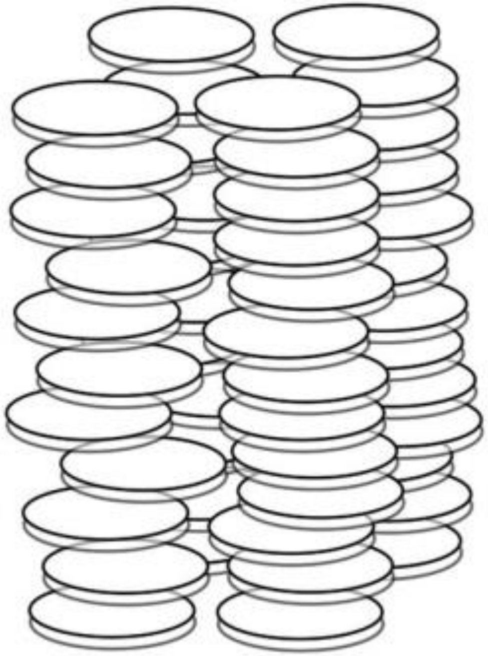
TYPES



smectic

- **Smectics:** The smectic phase of liquid crystal, is characterized by a slight degree of translational order in the crystal molecules. In this phase the molecules tend to line themselves up into layers. While these layers as a whole move freely, movement within the layers is restricted.

TYPES



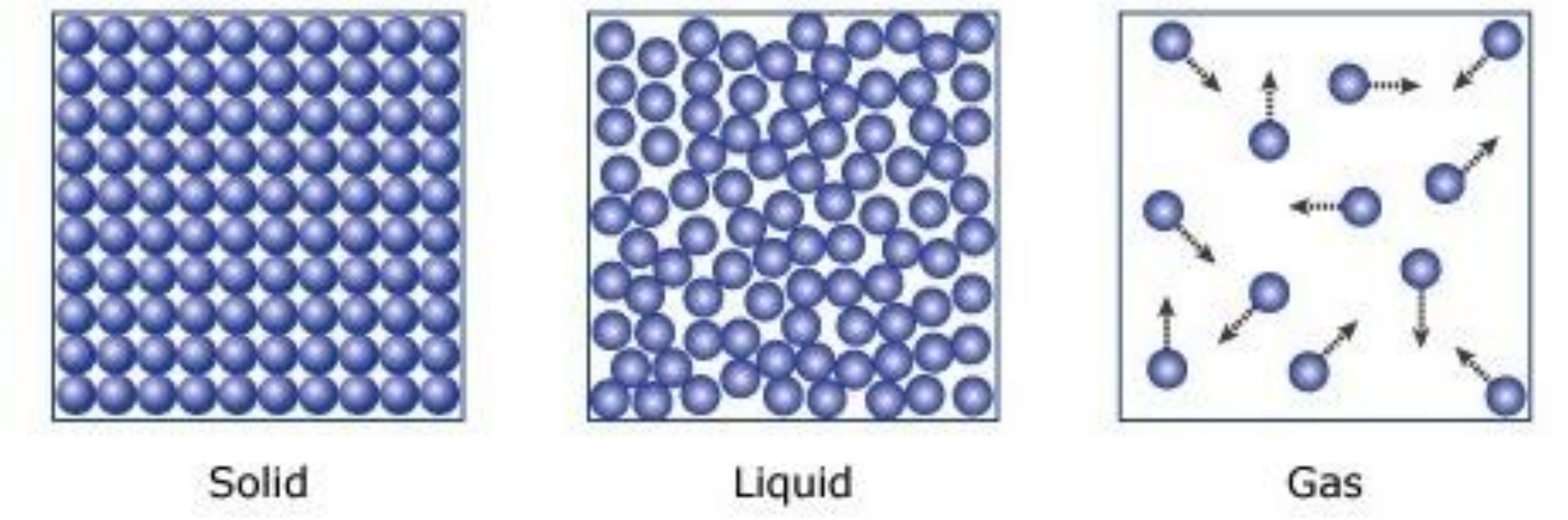
columnar

- **Columnar:** Columnar mesophases are often formed by disc-shaped molecules. The most common arrangements of columns in two-dimensional lattices are hexagonal, rectangular, and herringbone. In the herringbone mesophase molecules are tilted with respect to the columnar axis.

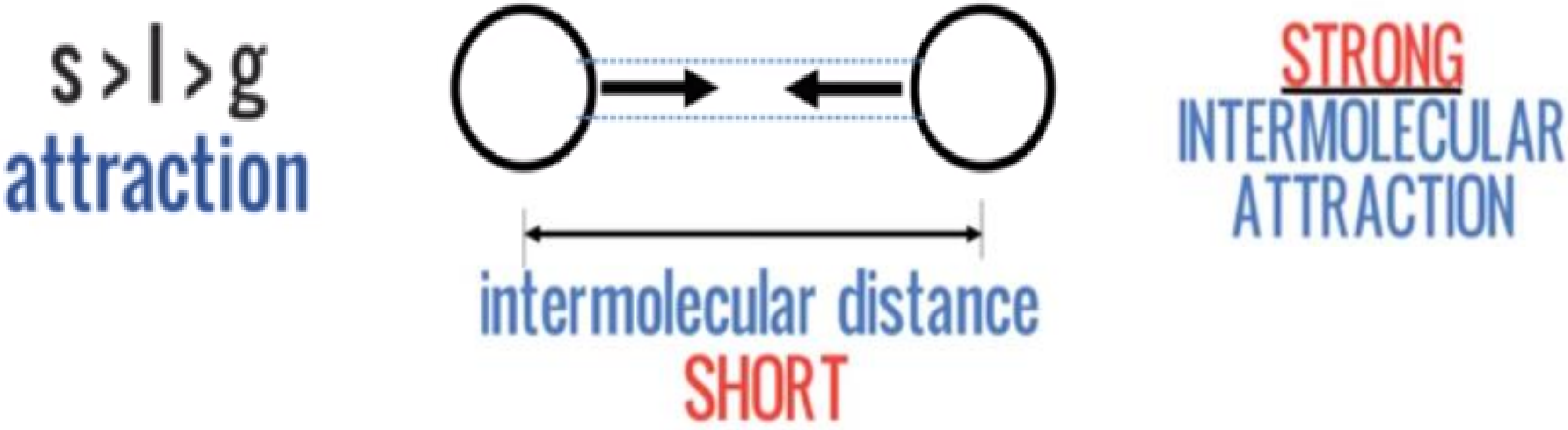
USES

- As a temperature sensor in thermometer
- To find the point of potential failure in electrical circuits
- To locate blockage in vein, arteries, infections, tumors by skin thermograph
- In display of electrical devices like digital watches, calculators and computers
- As a solvent in chromatography

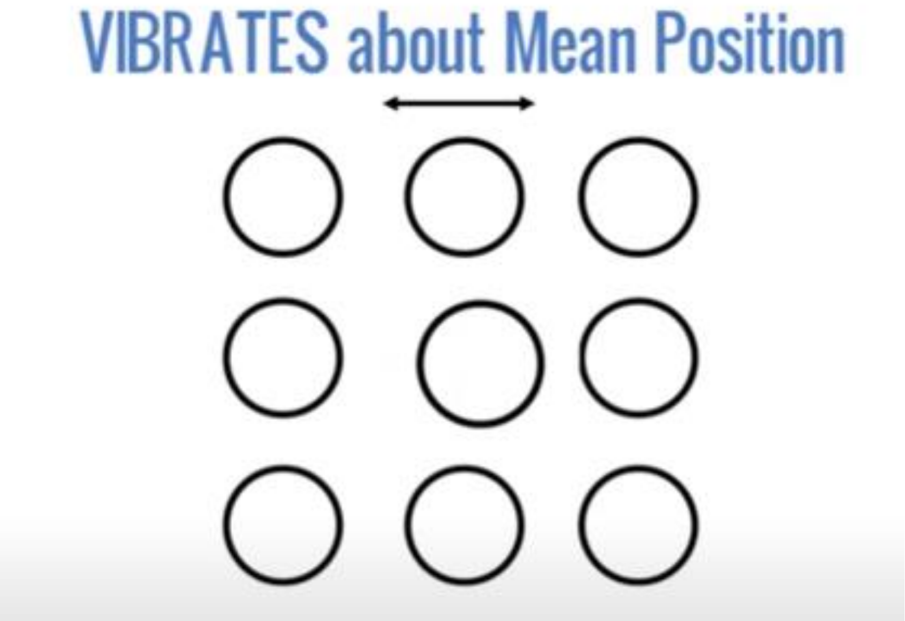
THE SOLID



- Solids have a definite shape, as well as mass and volume, and do not conform to the shape of the container in which they are placed.
- Solids also have a high density, meaning that the particles are tightly packed together.

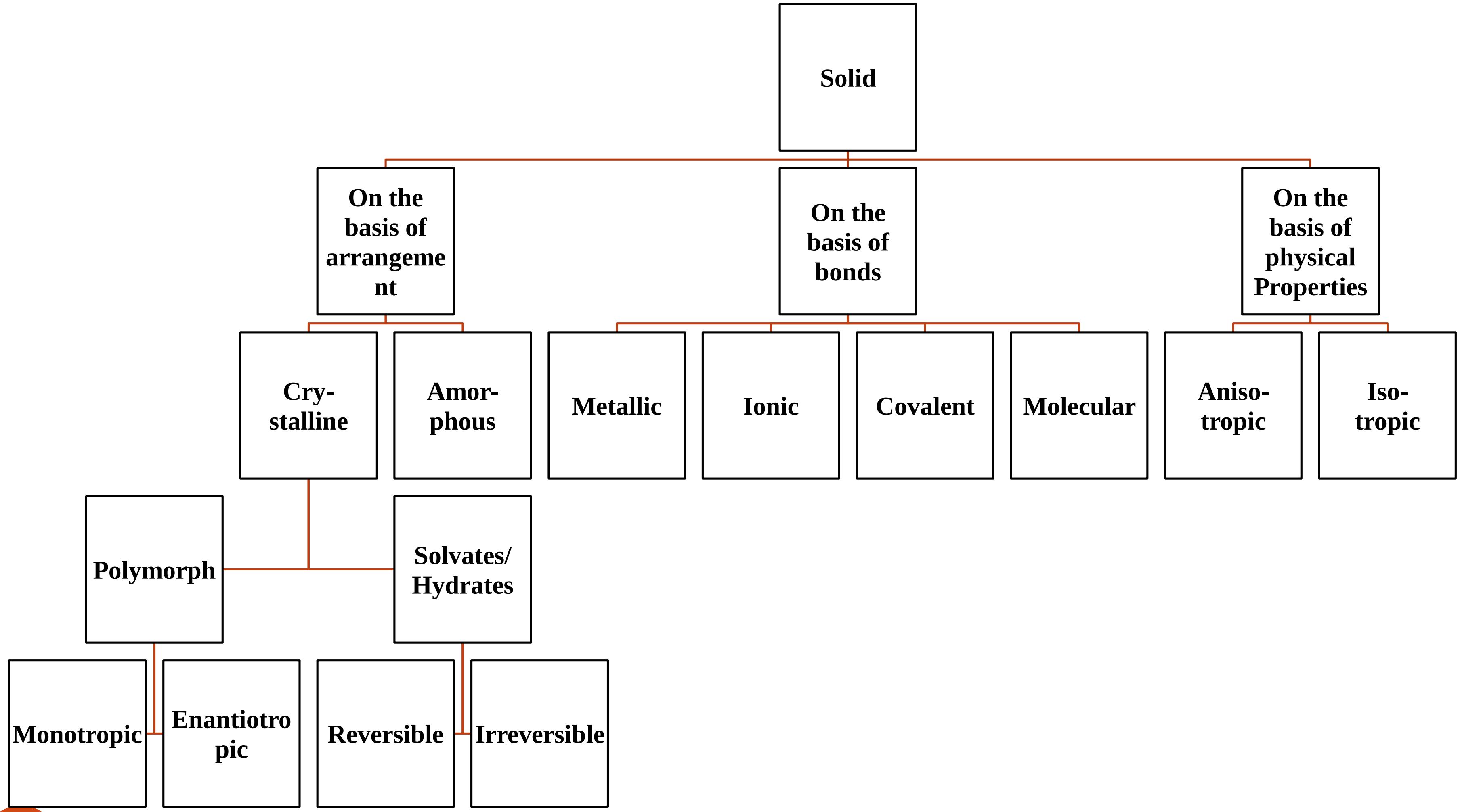


- In a solid, particles are held tightly together by strong chemical forces so they don't move much.
- The attraction between individual atom or molecule that constitutes a solid is on high in comparison to liquid and gas.
- The strong intermolecular attraction hold every atom or molecule tightly reducing the intermolecular distance.

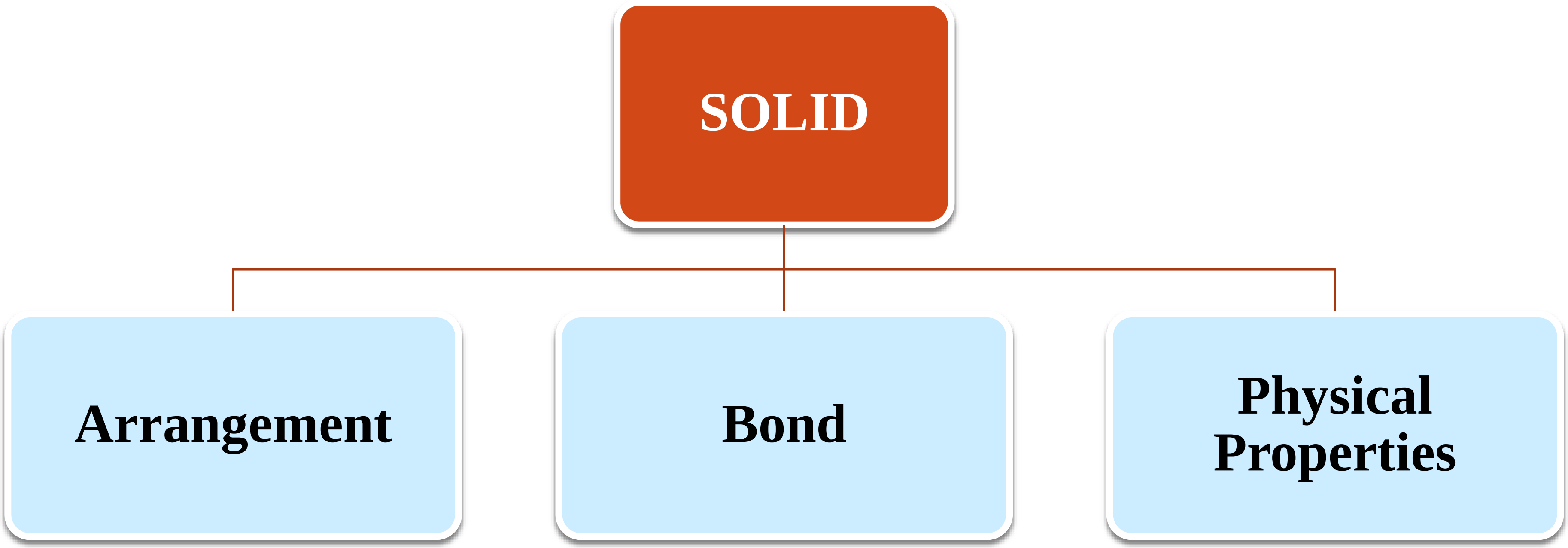


- The electrons of each atom are constantly in motion, so the atoms have a small vibration, but they are fixed in their position. Because of this, particles in a solid have very low kinetic energy.

CLASSIFICATION



- Solid
  - On the basis of arrangement
    - Cry-stalline
      - Polymorph
        - Monotropic
        - Enantiotropic
      - Solvates/ Hydrates
        - Reversible
        - Irreversible
    - Amor-phous
  - On the basis of bonds
    - Metallic
    - Ionic
    - Covalent
    - Molecular
  - On the basis of physical Properties
    - Aniso-tropic
    - Iso-tropic

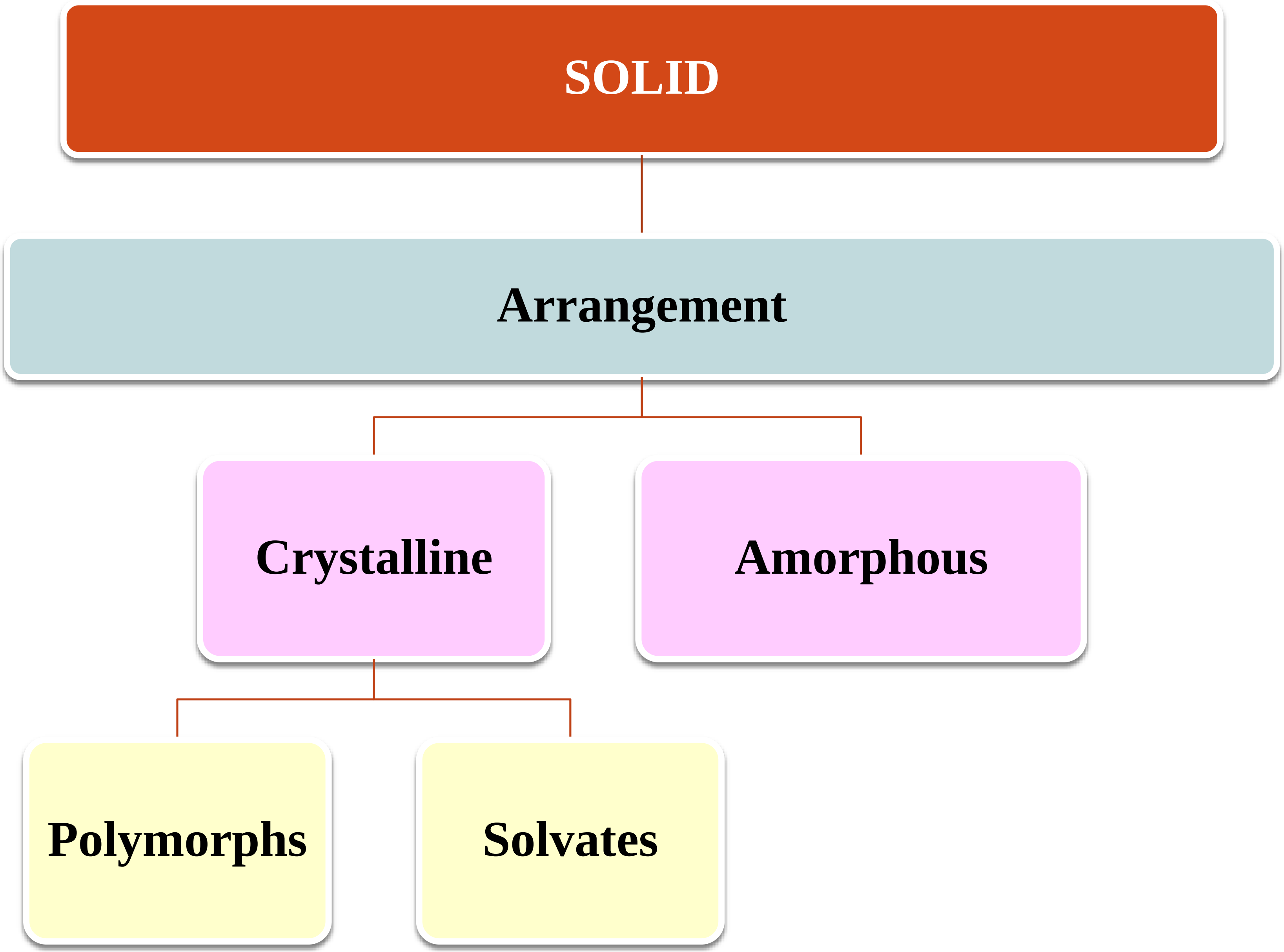


SOLID

Arrangement

Bond

Physical Properties



SOLID

Arrangement

Crystalline

Amorphous

Polymorphs

Solvates

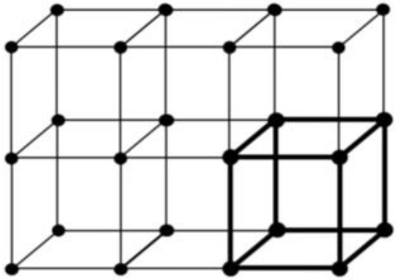
- **Crystalline:**

  - These types of solids are characterised by definite geometric shape.

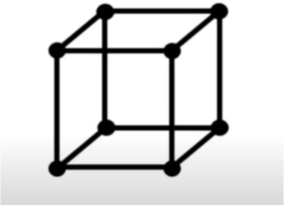
  - They are again sub classified as polymorphs and solvates or hydrates.

  - Polymorphs are the crystalline solids which show different crystalline forms for same chemical composition.

  - Solvates or hydrates are the molecular complex that has incorporated the crystallizing solvent within crystal lattice.

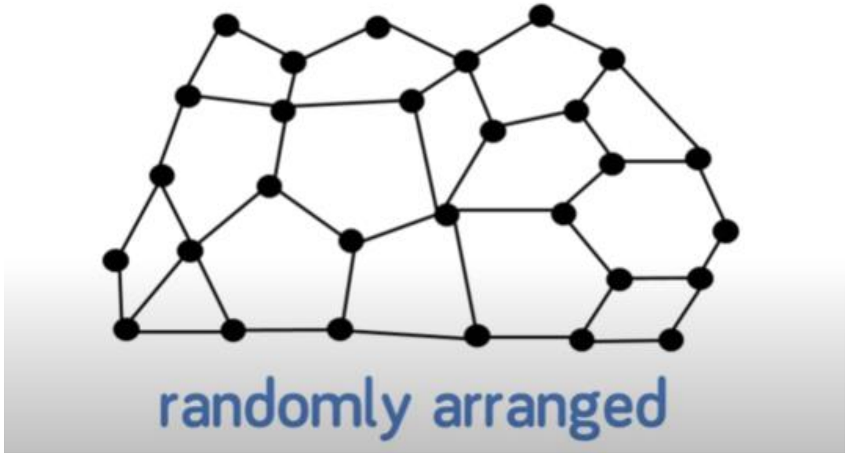


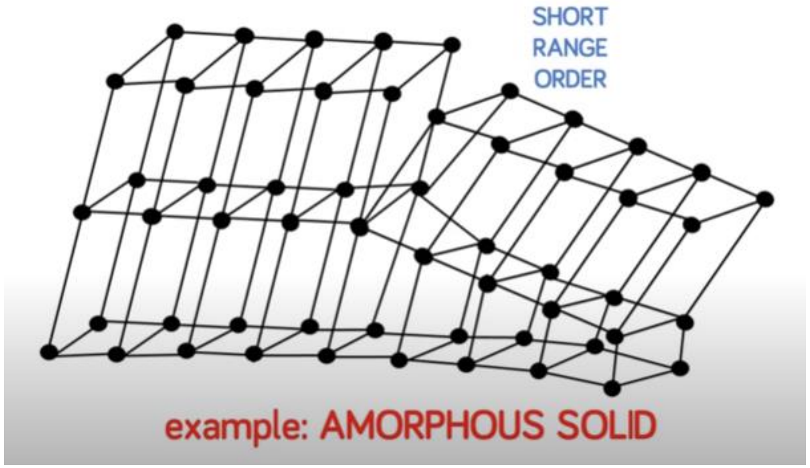
definite arrangement

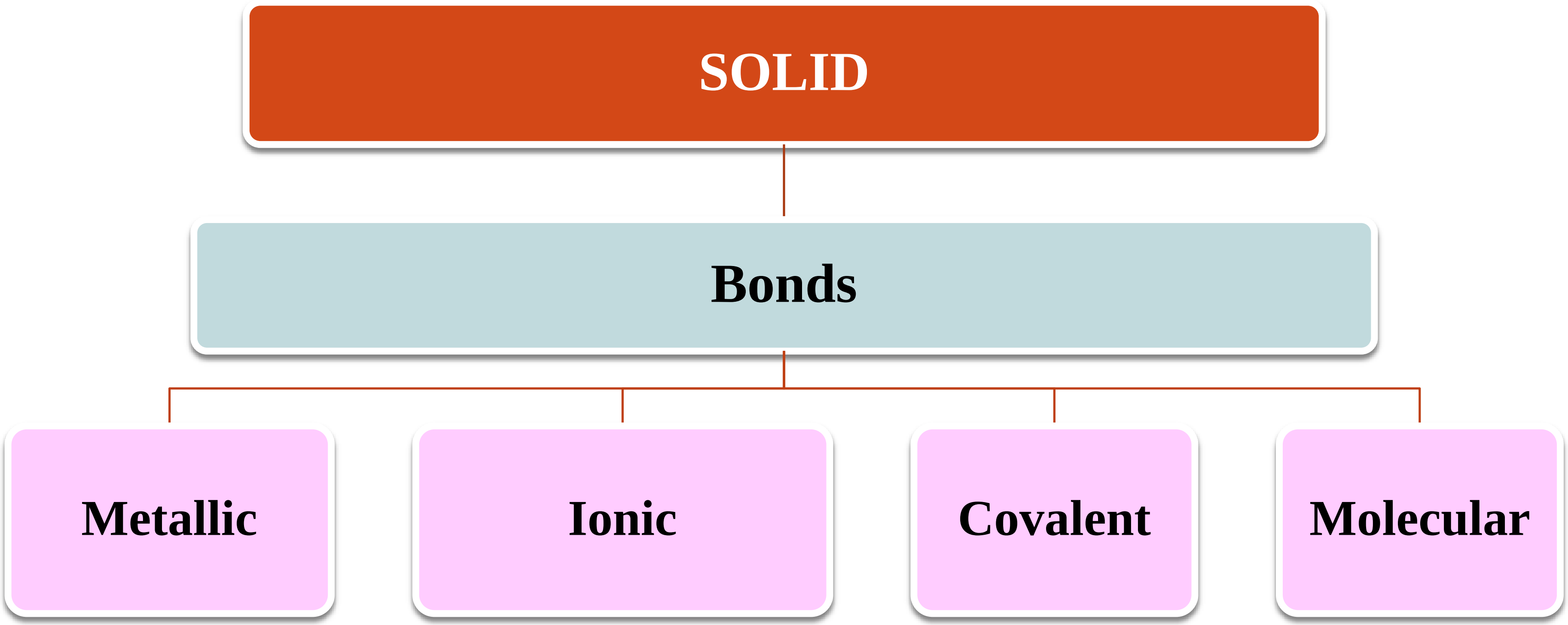


- **Amorphous:**

  - The constituents in this class of solid are arranged randomly in disordered structure.







SOLID

Bonds

Metallic

Ionic

Covalent

Molecular

- Based on the nature of bonds, solids may be classified in the order of decreasing strength as:
- **Metallic Solids:**

- Metallic crystalline solids feature atoms that are held together by metallic bonds, which are electromagnetic in nature.
- These bonds give metallic crystalline structures their distinctive qualities of being ductile, malleable and strong conductors of heat and electricity.
- These are the good conductors of heat and electricity.
- They have cubic closed packed or hexagonal closed packed unit cells.
- Common examples include zinc (Zn) and iron (Fe).

- **Ionic Solid:**

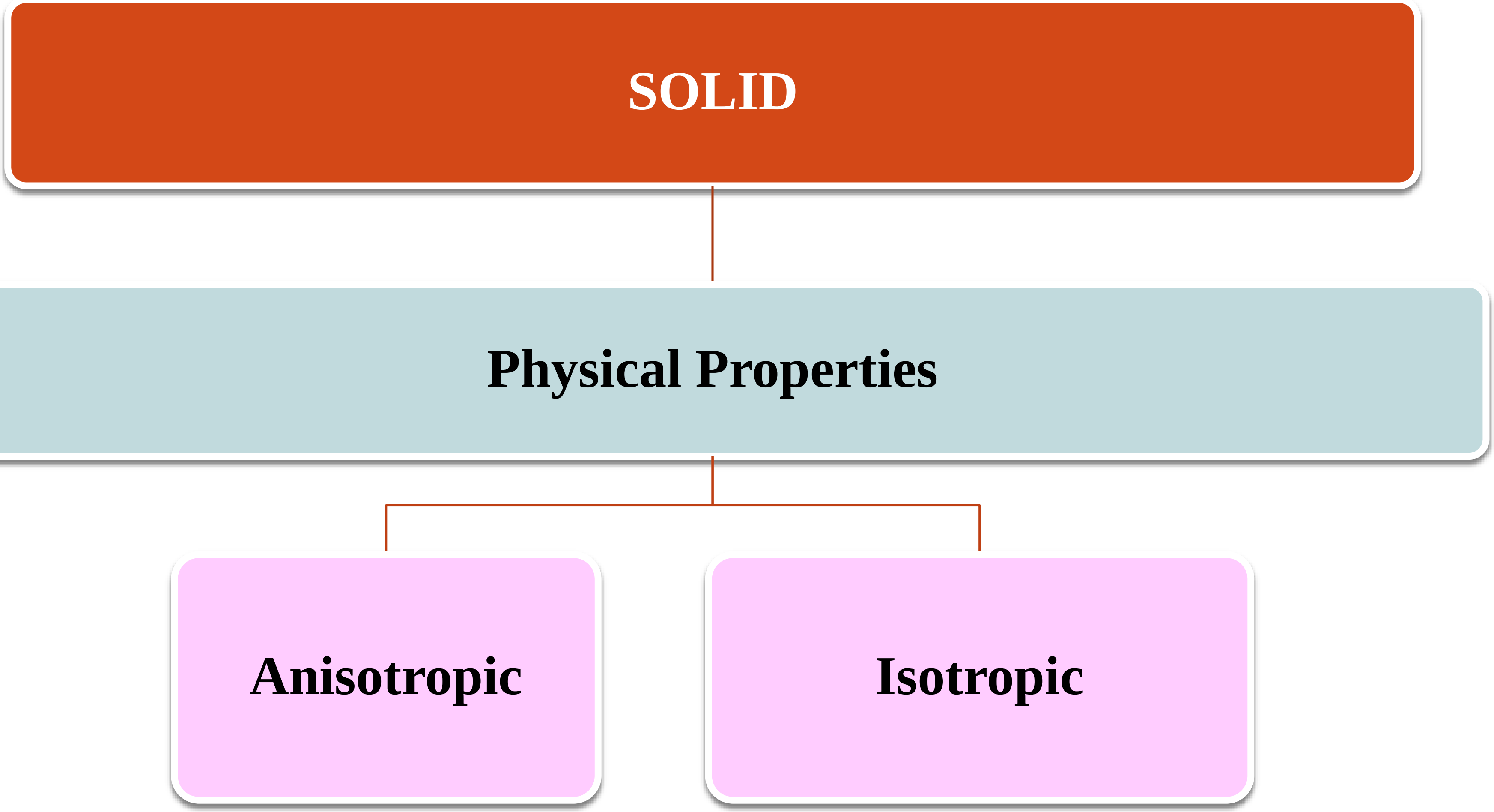
- In this type of solid, the unit constituents are ions which are held together by electrostatic forces of attraction maintaining overall electro neutrality.
- Ionic crystalline solids which are comprised of positive and negative ions held together by ion-ion attraction come in three basic forms: with trigonal holes, tetrahedral holes and octahedral holes.
- Because of the strong forces between the ions, Ionic crystalline solids are known for their high melting points and for being hard and brittle.
- Common examples include sodium chloride (NaCl), magnesium oxide (MgO) and calcium fluoride (CaF_2).

- **Covalent Solid:**

- These are also known as valence or atomic solids. The constituent units within the solid are attached either by covalent linkages or by Van der Waals forces between layers.
- Atomic crystalline solids consist of atoms that are held together by dispersion.
- These solids are soft, make poor electrical and thermal conductors and have low melting points. Common examples include quartz (SiO_2) and diamonds

- **Molecular:**

- Molecular crystalline solids are comprised of molecules, which are held together by dispersion (or London), dipole-dipole and hydrogen-bond inter-particle forces.
- These are all intermolecular forces, which are considerably weaker than intramolecular forces, such as ionic bonds.
- Molecular crystalline solids are fairly soft, make poor electrical and thermal conductors and have low to moderate melting points. Common examples include ice (H_2O) and dry ice (CO_2).



SOLID

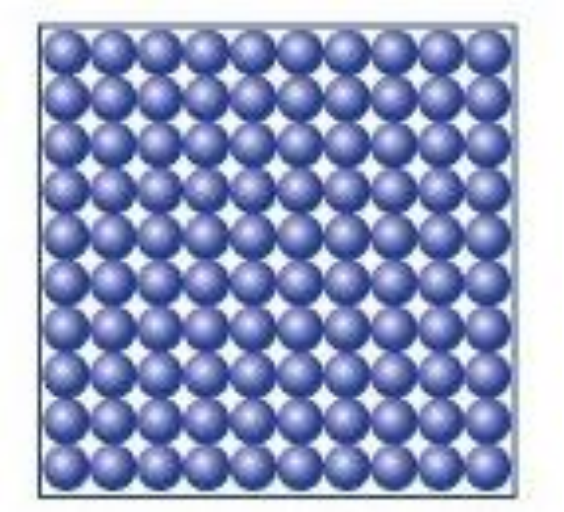
Physical Properties

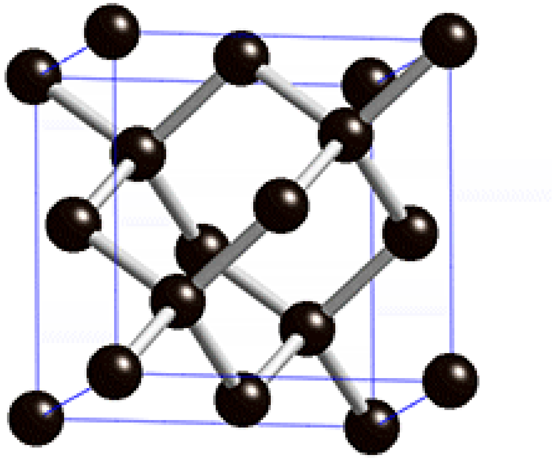
Anisotropic

Isotropic

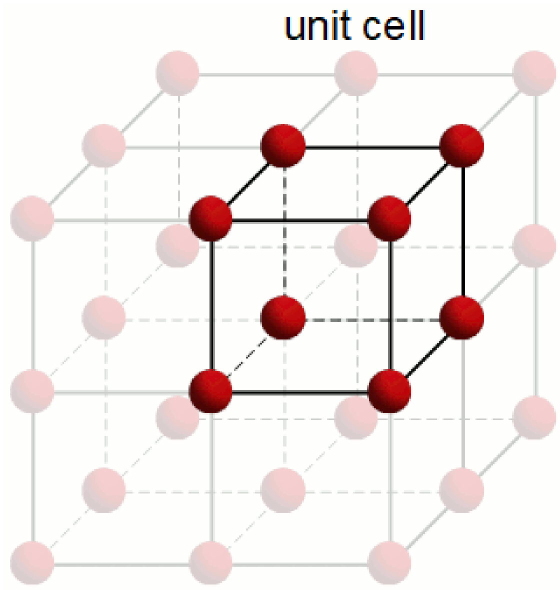
- Based on the physical properties, solids are classified as anisotropic and isotropic
- **Anisotropic:**
- These are the substances in which magnitude of physical property changes with direction.
- The phenomenon of having physical properties different in different directions in known as anisotropy and thus such solids are known as anisotropic substances.
- When light ray enters into anisotropic substance, it splits into two separate components which travel with different velocities.
- **Isotropic:**
- Iso means same. These are the substances which exhibit same value of any property in all directions.
- A phenomenon of having same physical properties in all directions is known as isotropy and thus such solids are known as isotropic substances.
- The properties are refractive index, mechanical strength, conductivities etc.

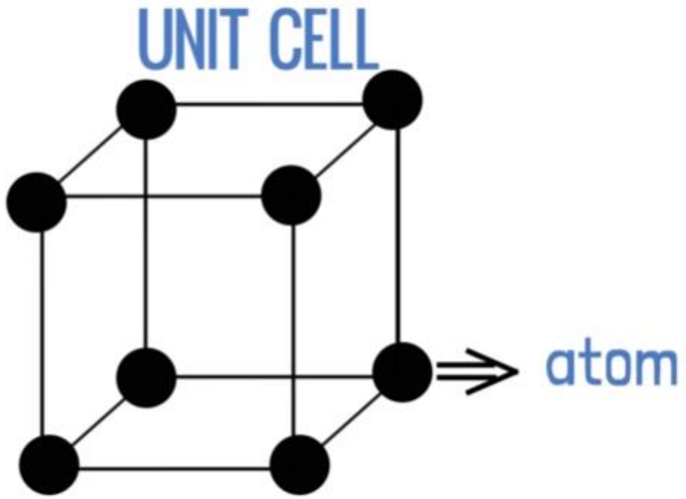
THE CRYSTALLINE SOLID





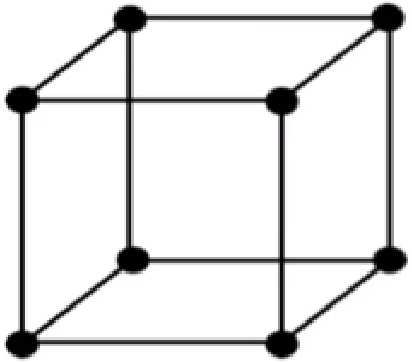
- Crystalline solid or a crystal is a solid material whose constituents, such as atoms, molecules or ions, are arranged in a highly ordered microscopic structure, forming a crystal lattice that extends in all directions.
- The majority of solids are crystalline solids, and the different arrangements of atoms and molecules within them can change their properties and appearance.

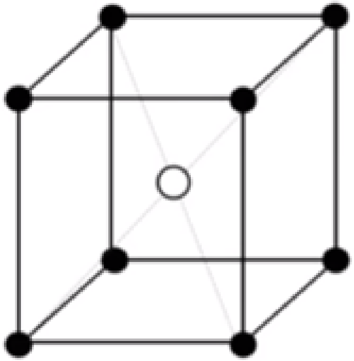


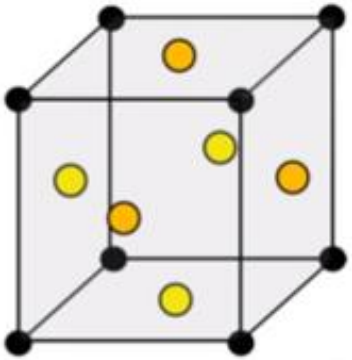


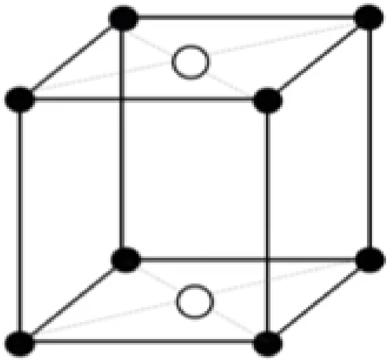
- The smallest unit of the structural pattern is called a unit cell.
- A crystal is made up of these identical unit cells repeated over and over in all three dimensions.
- A crystal structure is characterized by its unit cell.
- This cell is the most fundamental component of the crystal's structure, and determines some of its properties.

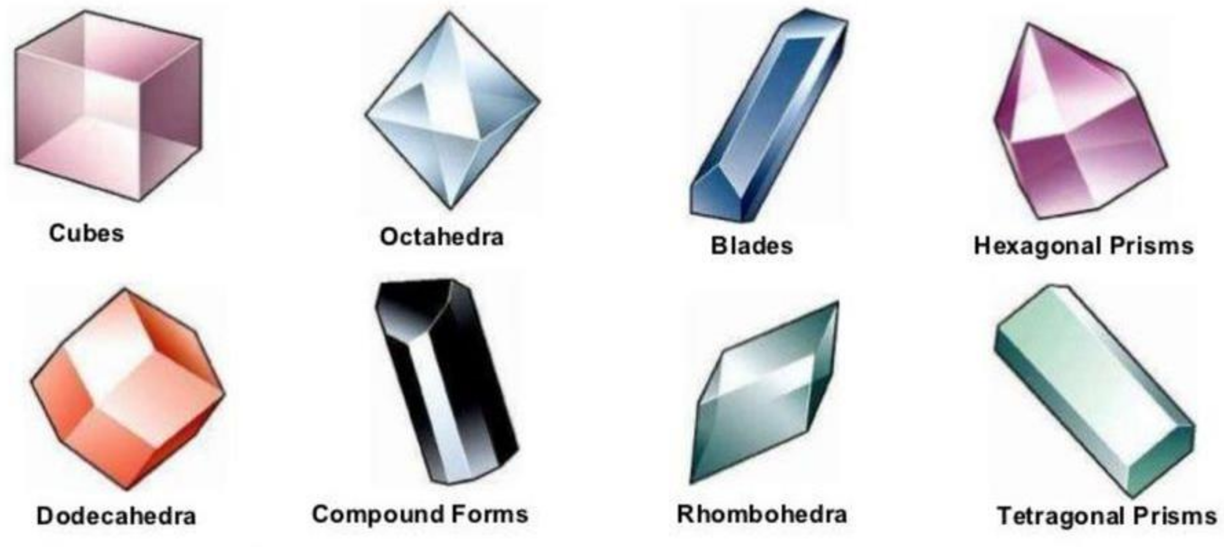
Types of Unit Cell


simple cubic


body centred

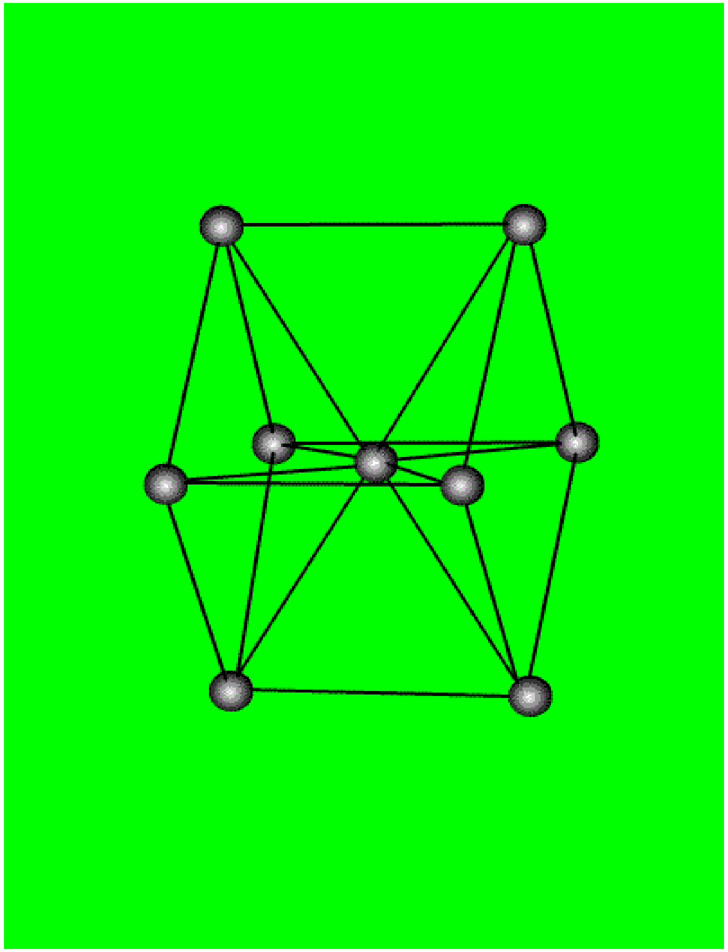

face centred


end centred



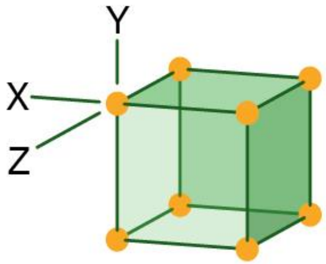
- Habit is the description of the outer appearance of a crystal whereas the internal structure is the molecular arrangement within the solid. The habit of crystal depends on the conditions of crystallization such as solvent used, temperature, concentration and presence of impurities in the solution.
- Changes in the internal structure usually alter the crystal habit. Single internal structure can have different crystal habit depending on environment.
- Crystal habit and the internal structure of solid can affect bulk and physicochemical properties which ranges from flowability to chemical stability.
- Crystal habit, Crystal Lattice and internal structure are known as the crystal parameters.

CRYSTALLOGRAPHY

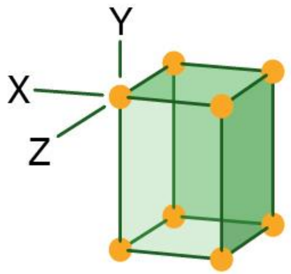


- The scientific study of crystals and crystal formation is known as crystallography. Crystallography is defined as the coordination of matter resulting from an orderly cohesive spatial arrangement of its component particles in space.
- Law of constancy of interfacial angles, Law of rational indices and Law of symmetry are the three laws of crystallography that are applied to deal with the interfacial angles and the rotational indices.

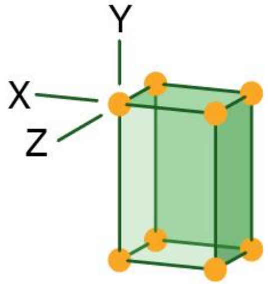
The seven primitive crystal systems



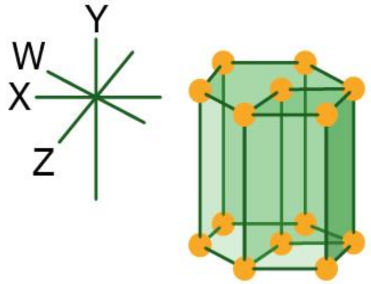
Isometric (or cubic)
All three axes are equal in length, and all are perpendicular to one another.



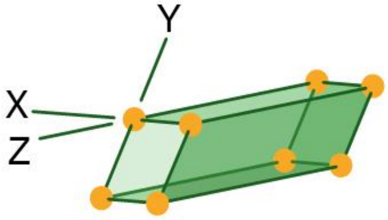
Tetragonal
Two of the three axes are equal in length, and all three axes are perpendicular to one another.



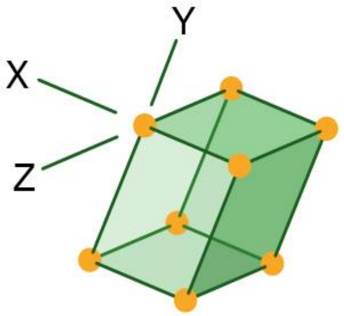
Orthorhombic
All three axes are unequal in length, and all are perpendicular to one another.



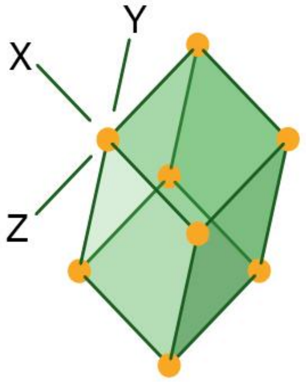
Hexagonal
Of four axes, three are of equal length, are separated by equal angles, and lie in the same plane. The fourth axis is perpendicular to the plane of the other three axes. Hexagonal cells have lattice points in each of the two six-sided faces.



Triclinic
All three axes are unequal in length, and none is perpendicular to another.

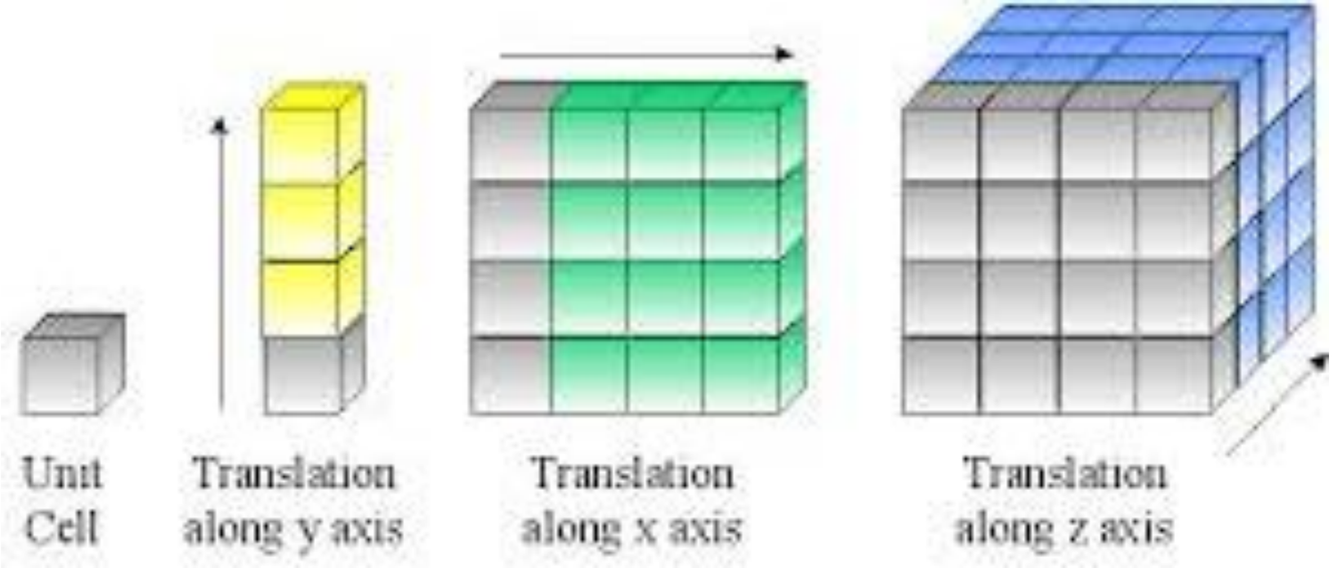


Monoclinic
All three axes are unequal in length, and two axes are perpendicular to each other.



Rhombohedral (or trigonal)*
All three axes are of equal length, and none of the axes is perpendicular to another, but the crystal faces all have the same size and shape.

CRYSTALLIZATION



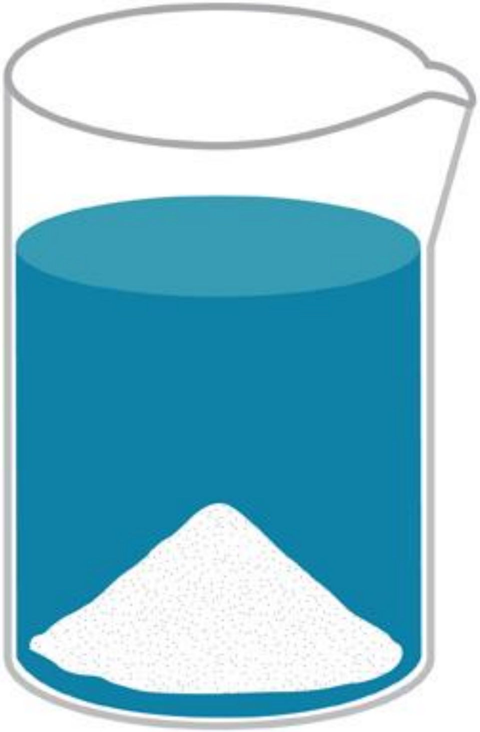
- The process of crystal formation via mechanisms of crystal growth is called crystallization or solidification. Crystallization is the dynamic process that signifies transition from disorder to perfection.
- The three step process of crystallization begins with nucleation followed by crystal growth and termination.

NUCLEATION

- Nucleation is a formation new solid phase either on an inert particle in solution or in solution itself. The equilibrium solution of solid and liquid is disturbed by cooling the solution or evaporating a part of solvent. The quantity of dissolved solid will exceed the equilibrium concentration and system will try to attain new state of equilibrium by precipitating solid in form of crystals. Atoms or molecules cluster together. When those clusters are stable enough and large enough, crystal growth begins.

CRYSTAL GROWTH

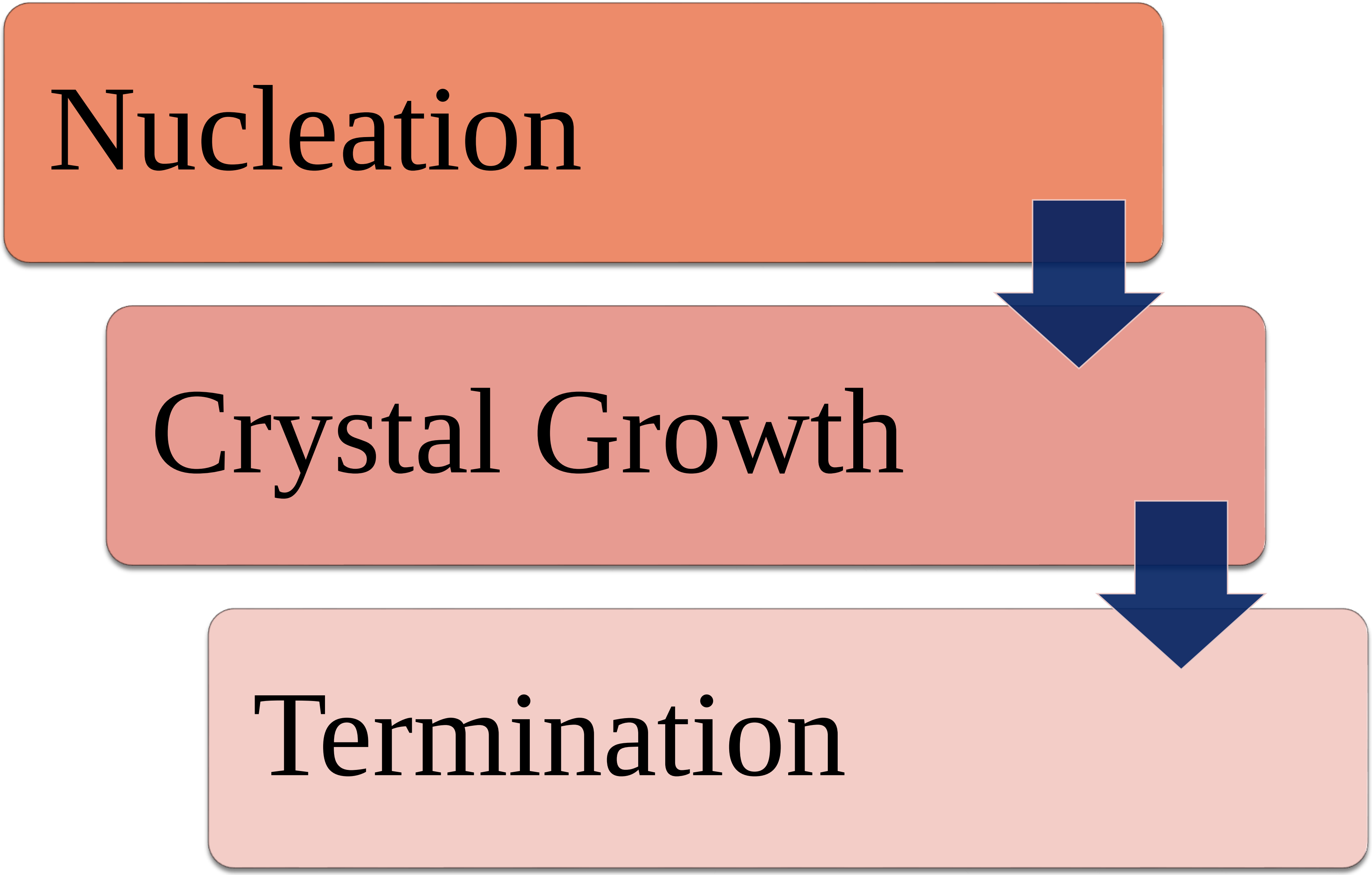
- Crystal growth is the process where a pre-existing crystal becomes larger in size with layer by layer addition of growth units.
- As a crystal grows, new atoms attach easily to the rougher and less stable parts of the surface, but less easily to the flat, stable surfaces.
- Therefore, the flat surfaces tend to grow larger and smoother, until the whole crystal surface consists of these plane surfaces. The growth of crystals generally occurs by means of following sequence of process either by diffusion of the molecules of the crystallizing substance through the surrounding environment or by diffusion of these molecules over the surface of the crystal to special sites on the surface. There is no limit to how large a crystal one can grow.



- **Supersaturation** is the driving force for both nucleation and crystal growth. Unless a solution is supersaturated, crystal can neither form nor grows. Supersaturation is the quantity of solute present in solution in which crystal are growing compared with quantity of solute that is in equilibrium with solution.
- **Mier and Issac** proposed a theory explaining relationship between Supersaturation and crystallization. The theory states that, “In a solution completely free from foreign particle spontaneous nucleation occurs at Supersaturation and not near saturation concentration.”

TERMINATION

- Termination in the final stage of crystallization process where crystal growth stops. At this stage the appearance of a crystal grown under specific conditions (known as habit) can be evaluated. The habit is evident in the relative development of the different faces of a crystal for a given material.

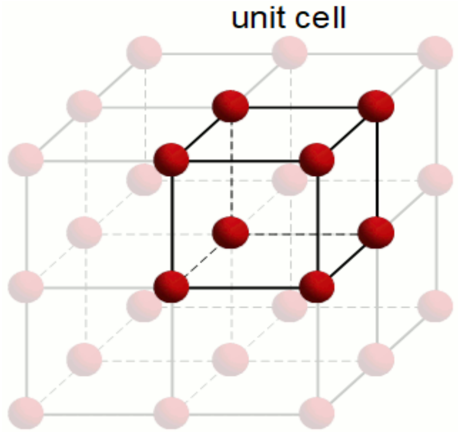


Nucleation

Crystal Growth

Termination

THE AMORPHOUS SOLID



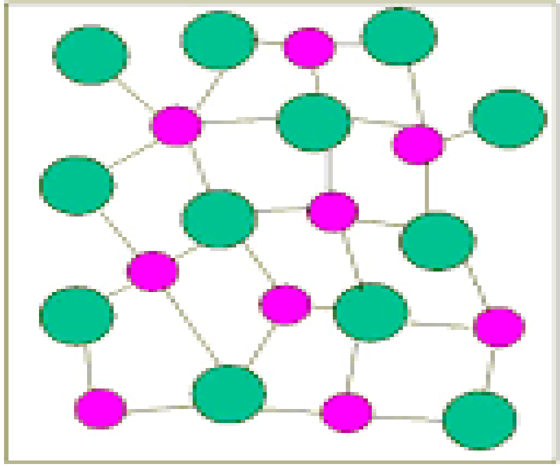

Galena

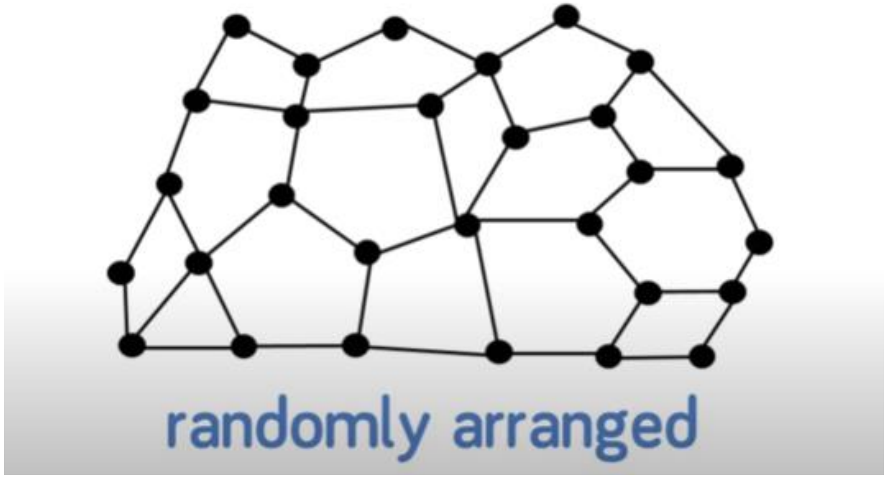

Quartz


Pyrite

- Amorphous solids are rigid structures but they lack a well-defined shape. They do not have a geometric shape. So they are non-crystalline. This is why they do not have edges like crystals do.
- The word amorphous comes from the Greek word ámorphos, which means "shapeless.“

Amorphous solid





- An amorphous solid is a solid whose atoms are not in an organized in a definite lattice pattern.
- An amorphous or non-crystalline solid is a solid that lacks the long-range order characteristic of a crystal. This means that the pattern of atoms or molecules in one place in the solid will look totally different from the pattern in another part of the solid.
- However, most amorphous solids do have short-range order.

- Amorphous solids do not have specific melting points and posses high aqueous solubility and dissolution than crystalline forms because there is no clear outline between their liquid phase and amorphous solid phase. Since the distance between neighbouring atoms or molecules varies over the whole material, thermal energy doesn't move through it evenly, which means it slowly softens over a wide temperature range rather than melting at one temperature.

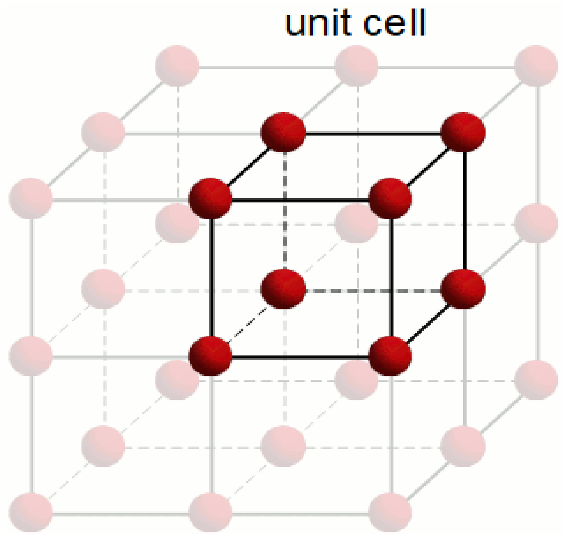
- Amorphous solids have two characteristic properties.
- When cleaved or broken, they produce fragments with irregular, often curved surfaces; and they have poorly defined patterns when exposed to x-rays because their components are not arranged in a regular array.

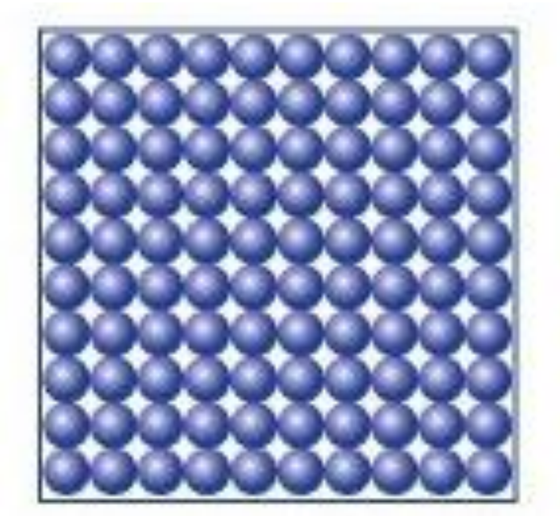
- Almost any substance can solidify in amorphous form if the liquid phase is cooled rapidly enough. Some solids, however, are intrinsically amorphous, because either their components cannot fit together well enough to form a stable crystalline lattice or they contain impurities that disrupt the lattice.

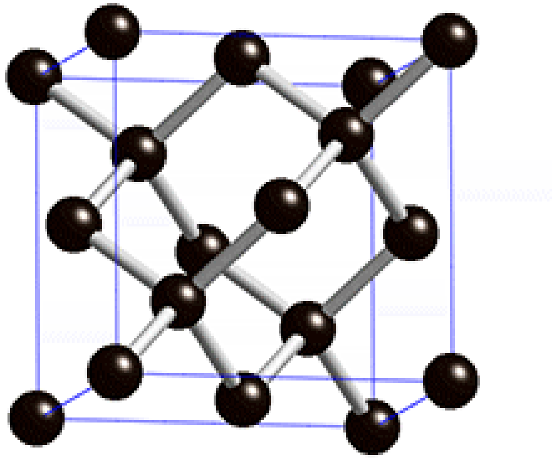
DIFFERENCE

CRYSTALLINE SOLID	AMORPHOUS SOLID
Crystals have definite and regular geometry	They do not have any definite geometry
Crystals have long range as well as short range order of constituent particles.	They have short range order
Crystals posses high melting points	They are lacking of sharp melting points
The crystals external forms have regularity	No external regularity in their form
They give a clean surface after cleavage	Amorphous solids exhibit irregular cut
They have definite heat of fusion	Amorphous solids do not possess any particular heat of fusion
Crystalline solids are considered as true solid	Amorphous solids are considered as super cooled liquids or also pseudo solids
Crystalline solids display anisotropism	Amorphous solids display isotropism

CRYSTAL ANALYSIS

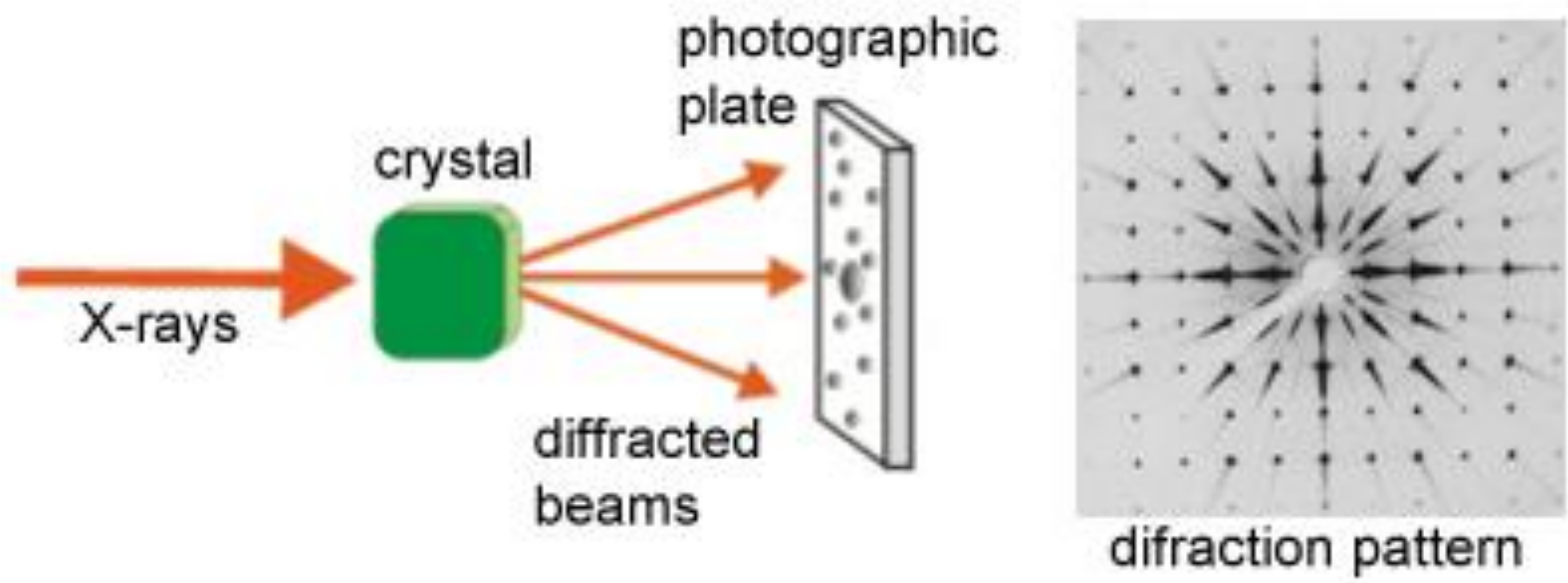






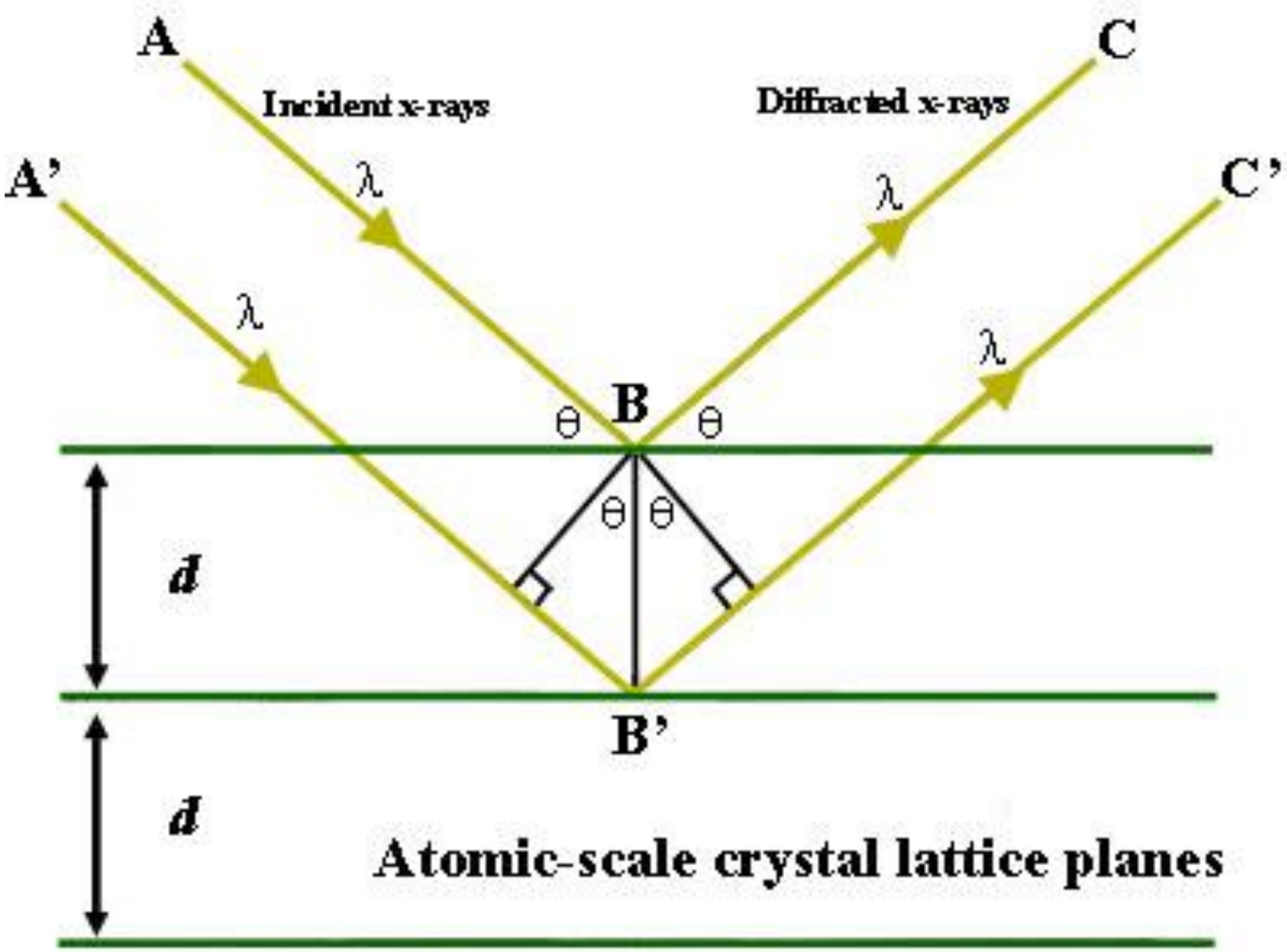
- A crystal lattice is considered to be made up of regular layer of planes of atoms at equal distances.
- Habit is the description of the outer appearance of a crystal whereas the internal structure is the molecular arrangement within the solid. The habit of crystal depends on the conditions of crystallization such as solvent used, temperature, concentration and presence of impurities in the solution.

X Ray Crystallography



- Since the wavelength of X ray is same as that of interatomic distance, Max von Laue, a German physicist suggested that crystal can act as a grating to X rays. Thus when a beam of X ray is allowed to fall on crystal a large number of images of different intensities are formed.
- If diffracted waves are in the same phase, they reinforce each other and series of bright spot are produced on photographic plate placed in path. If the diffracted waves are out of phase, interference will result and dark spots are observed on photographic plate.
- From overall diffraction pattern produces by crystal, we can get the detail information regarding position of particles in the crystal solid. Therefore the study of crystal structure with help of X ray is called X ray crystallography.

BRAGG's EQUATION



- In 1913 physicist Sir William Henry Bragg and his son Sir William Lawrence Bragg made successful attempt in determining the interatomic distance in a crystal lattice using X rays.
- According to Braggs, X ray obeys law of reflection and the extra distance travelled by the second ray is an integral number of wavelength.
- To illustrate this, consider a crystal with crystal lattice planar distances ‘d’. Where the travel path length difference between the ray paths ABC and A'B'C' is an integer multiple of the wavelength, constructive interference will occur for a combination of that specific wavelength, crystal lattice planar spacing and angle of incidence (θ). Each rational plane of atoms in a crystal will undergo refraction at a single, unique angle (for X-rays of a fixed wavelength).

- The general relationship between the wavelength of the incident X-rays, angle of incidence and spacing between the crystal lattice planes of atoms is known as Bragg's Law, expressed as:

$$n\lambda = 2d\sin\theta$$

where,

n (an integer) is the "order" of reflection,

λ is the wavelength of the incident X-rays,

d is the spacing between the planes in the atomic lattice,

θ is the angle between the incident ray and the scattering planes.

X RAY CRYSTALLOGRAPHY METHODS

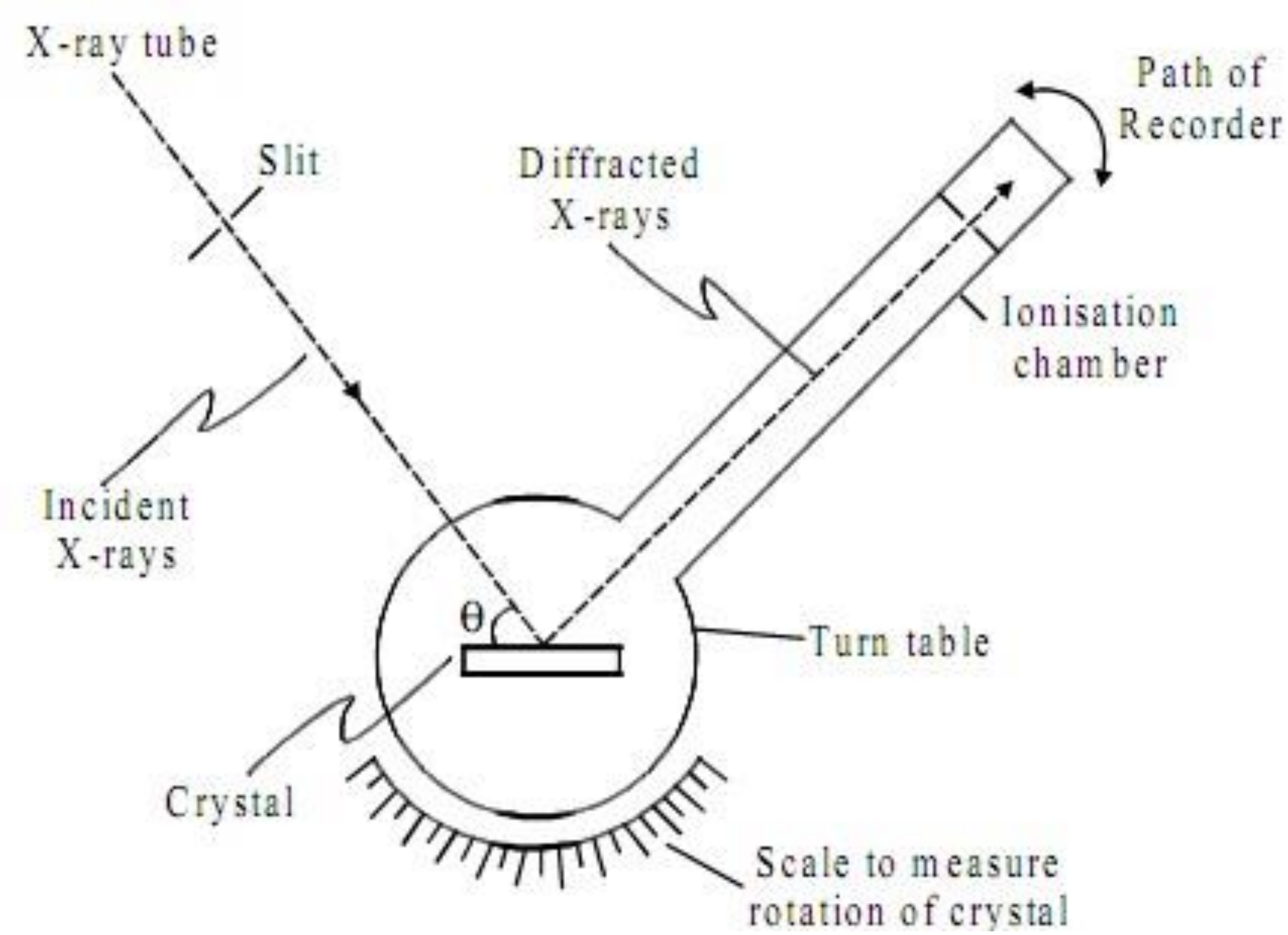
- Detailed structural characterization of coordination compounds is usually carried out by diffraction methods, which can provide not only information on composition and molecular connectivity, but also full geometrical parameters.
- The most widely used methods are

    - rotating crystal method

    - powder method.

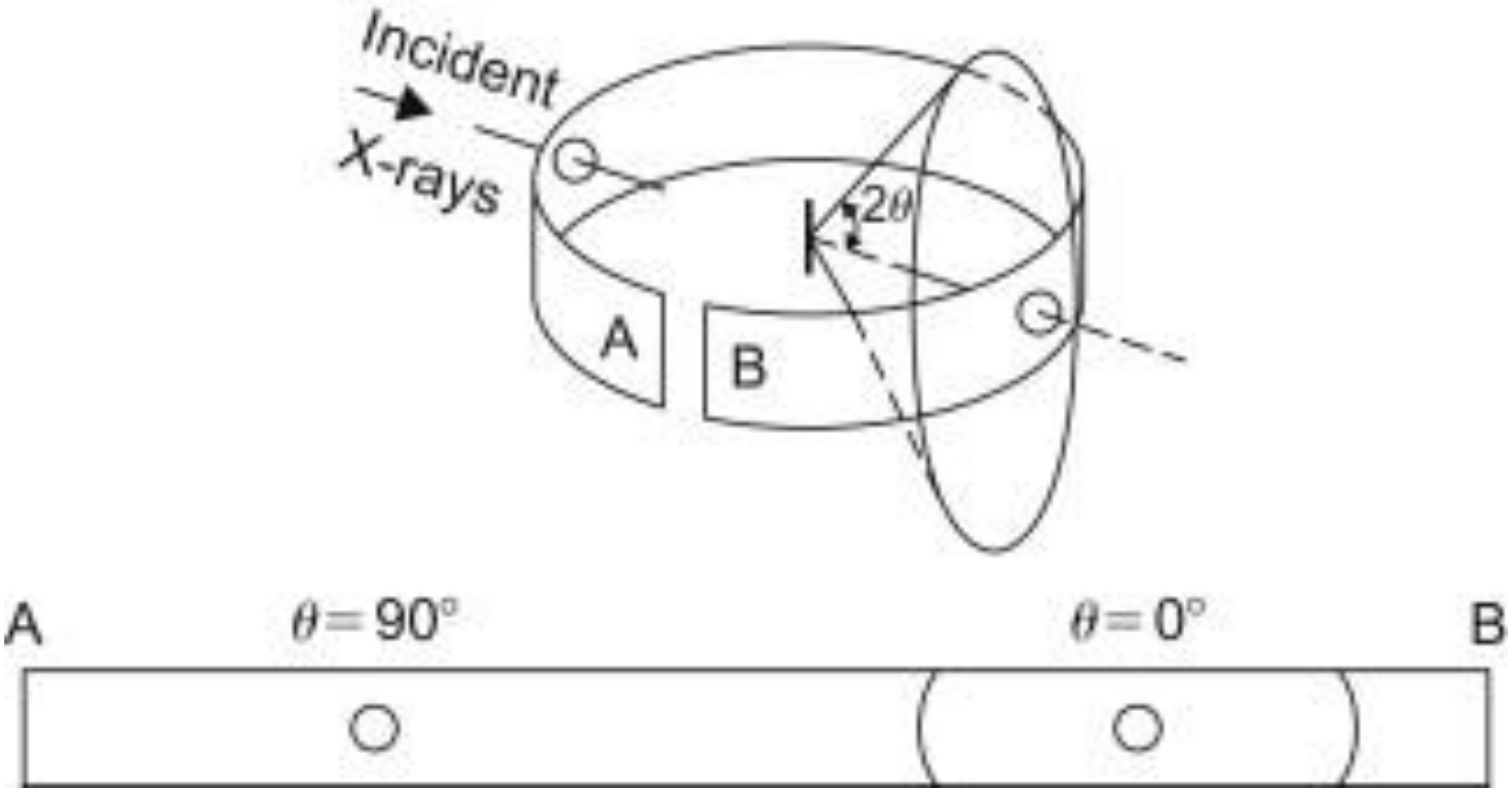
ROTATING CRYSTAL METHOD

- In this method a beam of X ray of known wavelength is passed through slit so as to obtain a narrow beam, which is then allowed to strike a single crystal mounted on the turntable.
- The crystal is rotated gradually by means of the turntable so as to increase the gleaning angle at which the X rays incident at the exposed face of crystal.
- The intensities of the reflected rays are measured in a recording device such as photographic plate and an ionization chamber.
- The angle for which reflection are maximum give the values of θ. The obtained values of n, λ and θ are used to calculate d by using Bragg’s equation.

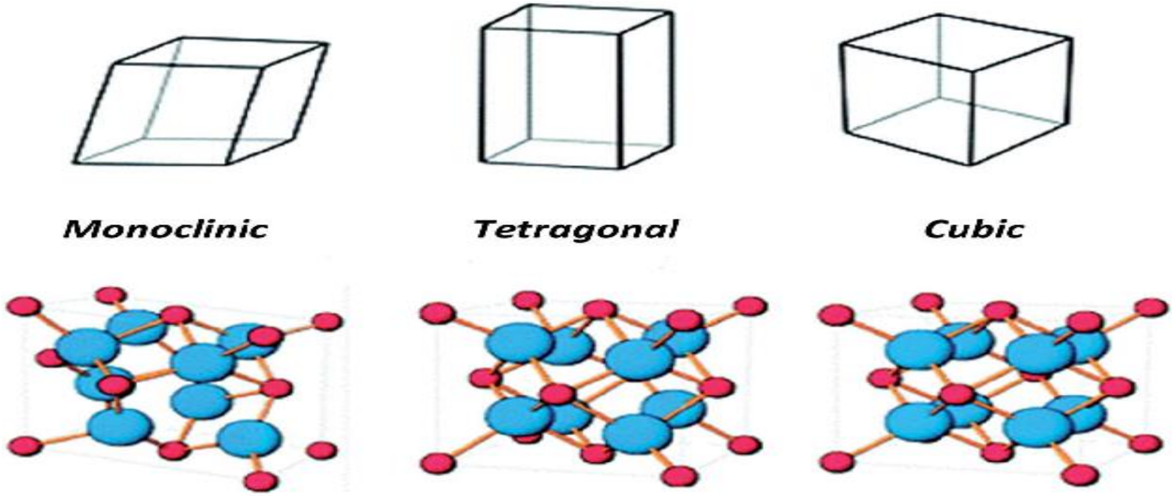

X-ray tube
Slit
Diffracted X-rays
Path of Recorder
Ionisation chamber
Incident X-rays
θ
Turn table
Crystal
Scale to measure rotation of crystal

POWDER METHOD

- The powder method, devised independently by Debye and Scherrer, is probably the most generally useful of all the X-ray techniques.
- It employs monochromatic radiation and a finely powdered, or fine-grained polycrystalline, wire specimen.
- In this case, θ is the variable, since the collection of randomly oriented crystals will contain sufficient particles with the correct orientation to allow reflection from each of the possible reflecting planes, i.e. the powder pattern results from a series of superimposed rotating crystal patterns.
- The angle between the direct X-ray beam and the reflected ray is 2θ, and consequently each set of crystal planes gives rise to a cone of reflected rays of semi-angle 2θ, where θ is the Bragg angle for that particular set of reflecting planes producing the cone.
- Thus, if a film is placed around the specimen, as shown in Figure, the successive diffracted cones, which consist of rays from hundreds of grains, intersect the film to produce concentric curves around the entrance and exit holes.


Incident
X-rays
2θ
A
B
A
θ = 90°
θ = 0°
B

POLYMORPHISM

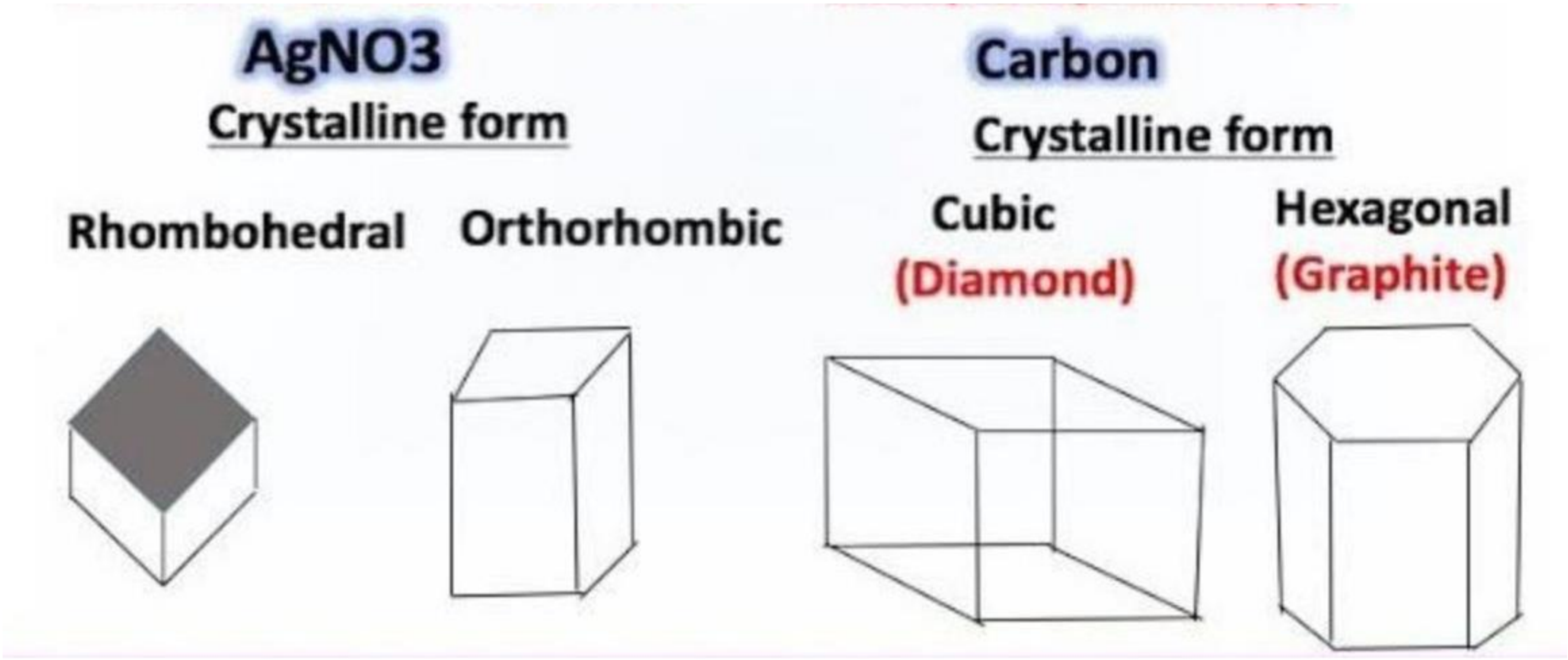


- Differences in the crystalline forms of many elements and compounds were discovered during the 1820s by Eilhardt Mitscherlich, a German chemist.
- ‘Polymorphism’ comes from the Greek word, Polus = many and morph = shape.
- Polymorphism is defined as the ability of a compound to crystallize in two or more crystalline forms with different internal lattices.

EFFECT of POLYMORPHISM

- As a result of polymorphism, molecules have different arrangements in the unit cell of its crystal and thus display different physicochemical properties.
- These include different packing properties, thermodynamic properties such as solubility, free energy, melting point, etc., spectroscopic properties, kinetic properties such as dissolution rate, stability, and mechanical properties such as hardness, compatibility, tableting, tensile strength, etc.

ALLOTROPY



- If the polymorphism exist in elemental solid and element crystallises in more than one distinct crystalline form, this phenomenon is known as *Allotropy*. For example carbon exist as cubic, diamond or hexagonal graphite.

REASONS OF POLYMORPHISM

- It essentially means that in different polymorphs, the same molecule exists in different ways.
- If this difference is because of packing, it is termed as packing polymorphism and if it is due to difference in conformation, it is called conformational polymorphism.
- In pseudopolymorphism the different crystal types are the result of hydration or solvation. This is more correctly referred to as solvomorphism as different solvates have different chemical formulae.

TYPES OF POLYMORPH

- Polymorphism can be classified into two types according to their stability with respect to the different range of temperature and pressure.
- Polymorphism is categorized into two types, Monotropic system and enantiotropic system.

a) Monotropic System:

When only one polymorphic form is stable at all temperatures below the melting point, with all the other polymorphic forms being unstable these polymorphs are said to be Monotropic.

e.g. metolazone

b) Enantiotropic System:

If one of the polymorphic form is stable (i.e., has lower free energy content and solubility) over a certain temperature range and pressure, while the other polymorphic form is stable over a different temperature range and pressure, then the two polymorphs are said to be enantiotropic.

e.g. carbamazepine and acetazolamide.

STABILITY OF POLYMORPH

- Out of polymorphs the form for which free enthalpy is low at given temperature and pressure are thermodynamically stable and other forms are said to be in metastable state.
- Polymorphs are designated by Roman numbers in order of their stability at room temperature. Form I usually has the highest melting point whereas other forms are further categorized as unstable and metastable.
- Unstable form readily converts into stable form and metastable form slowly converts into stable form.
- The particular advantage of polymorphism is that the chemical identity of the material remains unchanged from one polymorph to another, so that a direct correlation between activity and solid state structure may be made.

- The relative stability and driving force for the polymorphic transformations at constant temperature and pressure is determined by Gibbs Free Energy (ΔG); the internal energy available for chemical work as given in equation

$$\Delta G = \Delta H - T\Delta S$$

Where,

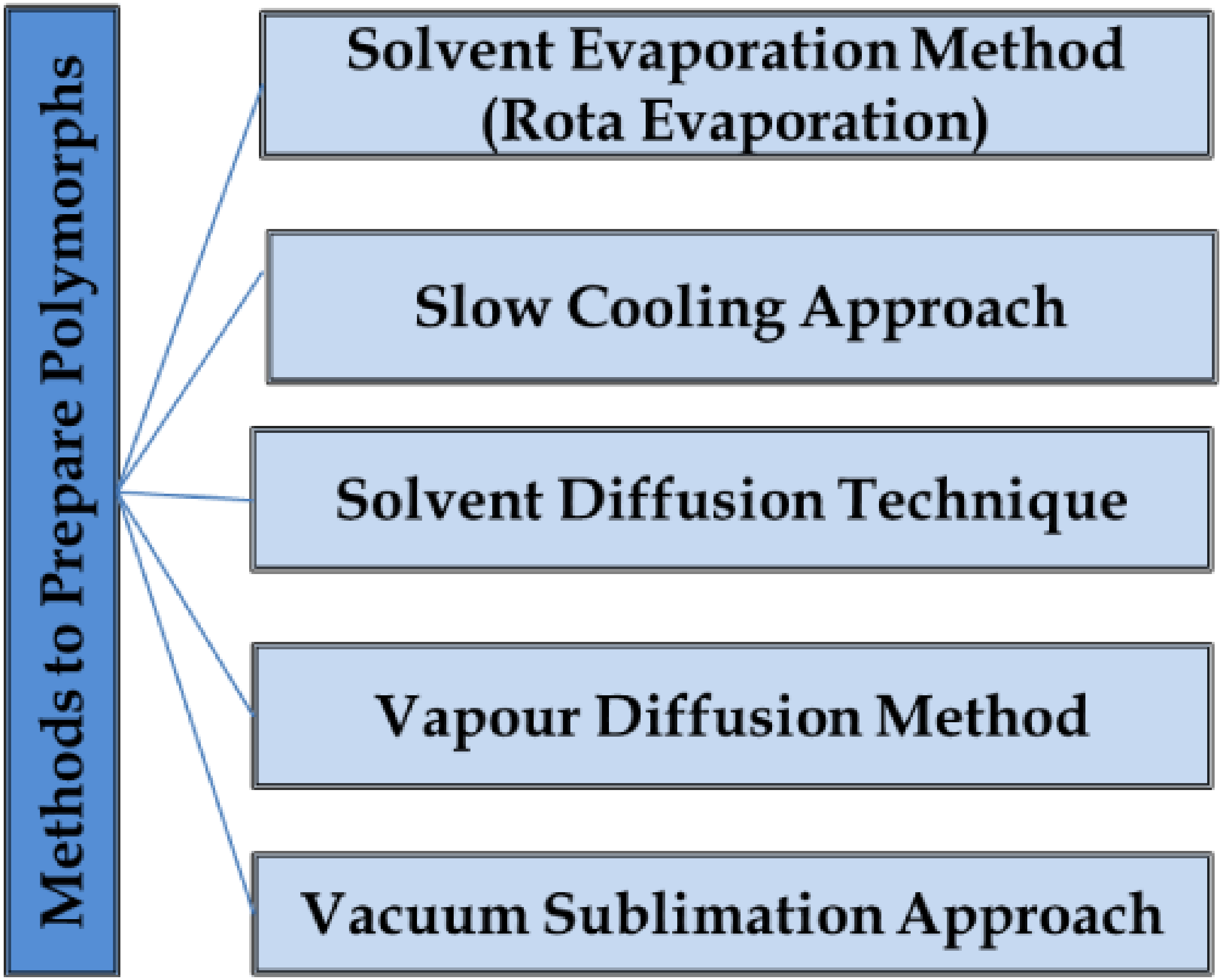
ΔH signifies the enthalpy change,

ΔS accounts for the entropy change,

T is temperature

- Negative value assures the spontaneity of the polymorphic transition whereas positive value renders the process non spontaneous.

METHODS OF POLYMORPH PREPARATION



Methods to Prepare Polymorphs

- Solvent Evaporation Method (Rota Evaporation)
- Slow Cooling Approach
- Solvent Diffusion Technique
- Vapour Diffusion Method
- Vacuum Sublimation Approach

Sr. No	Method	Characteristics	Advantages	Disadvantages
1	Solvent Evaporation	Applicable for high melting substances	High purity and yield	Desirability of recrystallization, small production volume and expensive
2	Slow cooling approach	First choice due to the ease and simplicity	Large scale production and easily reproducible	Low yield, higher input, chances of disordered/twinned crystals
3	Solvent diffusion technique	Best for less quantity of substance and the materials sensitive to air and moisture	Larger surface area, higher solubility, high mechanical strength to crystals	Low production yield, tedious solvent selection
4	Vapor diffusion method	Requires less amount of sample	Less quantity of sample for crystallization	Time consuming, difficult solvent selection, expensive and low yield
5	Vacuum sublimation method	Desired when quantity is less and the sample is thermolabile	Excellent crystal variety	Disordered or twinned crystals

- **Solvent evaporation method (Rota Evaporation):**

  In this approach, the saturated solution of the drug is prepared in an appropriate solvent and the solvent is removed by rotatory evaporation. Air drying at various temperatures, can also be employed to obtain different potential polymorphs.

- **Slow cooling approach:**

This technique is frequently employed for the polymorphic forms of less soluble drugs in the solvent systems having boiling point range of 30 to 90°C. In brief, the solute is heated in the solvent just above the boiling point of the latter to produce the saturated solution. This solution is transferred to a stoppered tube and is connected to a Dewar flask containing water at a temperature just below the boiling point of the solvent. The Dewar flask is left in these conditions for several days. This technique may further be improved to obtain better crystal forms using different solvent mixtures of different polarities. Variation in the solvent composition may inhibit or promote growth of particular crystal faces and hence, can yield crystals of the desired morphology. This approach is also called the solution growth approach.

- **Solvent diffusion technique:**

This method is employed when the amount of drug available is less, and the drug is sensitive to air and/or solvent(s). In this option, the solution is placed in a sample tube; subsequently a less dense solvent is carefully dripped down the sides of the tube using either a pipette or a syringe to form a discreet layer. The slow diffusion of the solvent results in the crystallization of API at the interface. Most employed solvent combination is CH_2Cl_2 / ethanol and is preferred one, provided the sample is insoluble in ether.

- **Vapor diffusion method:**

This method is analogous to the previous one and is also applicable for the less quantities of the sample. In this case, the concentrated drug solution (0.5 µL to approximately 20 µL) is placed as a drop hanging on the underside of a microscope cover slip. The cover slip with the hanging drop is sealed with silicon oil over a solution (approx. 1 mL; reservoir) containing high concentration of precipitant. Due to higher precipitant concentration, the latter has lower vapor pressure than the drug solution. This results in diffusion of the solvent from the drop towards the reservoir and subsequent crystallization of the API within hours to weeks.

- **Vacuum Sublimation**

Sublimation is known to offer excellent crystals of variety of compounds, especially the air sensitive ones. This approach is frequently employed to induce crystallization with numerous variations of static or dynamic vacuum. A small amount of sample sealed under vacuum in a reactor is generally subject to a temperature gradient in numerous manners. Temperature of the order of 250^{O}C can be easily employed at a pressure of around 10-2 mmHg. The crystal grows from the wall to the center of the reactor.

PHYSICOCHEMICAL PROPERTIES

By,

Dr. Vaibhav G. Bhamare

Ph D, M. Pharm, MBA

- **Physical Property:**

  - It can be measured or observed without changing composition of substance.

  - There are two types of

  a) Extensive Property

  b) Intensive Property

- **Chemical Property:**

  - This are the properties which can only be measured or observed through a change or attempt to change the chemical composition of a substance

  - The reason to have a change can either be intrinsic or extrinsic.

Physical vs. Chemical Change

Physical Change

- Atoms **do not** rearrange
- Only physical properties change. Chemical properties **do not** change.
- Physical changes are generally easy to **reverse**.
- No energy is **produced** by the substance.

Chemical Change

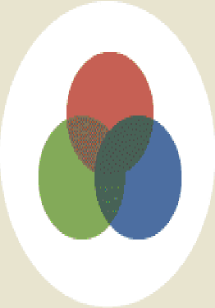
- Atoms are **rearranged** into different molecules
- **Both** physical and chemical properties are changed
- Changes are **not** reversible without another reaction
- **Energy** is often produced (fire or heat, for example)

INTENSIVE PROPERTIES
VS
EXTENSIVE PROPERTIES

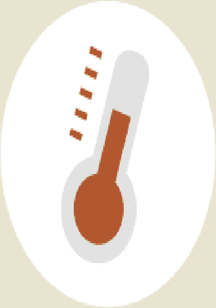
Intensive properties are physical properties that do not depend on the amount of matter	Extensive properties are physical properties that depend on the amount of matter
Independent of the amount of matter	Depend on the amount of matter
Some examples include melting point, boiling point, density, etc.	Some examples include volume, mass, energy, etc.

Intensive Properties

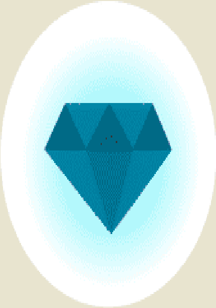
Boiling Point



Color



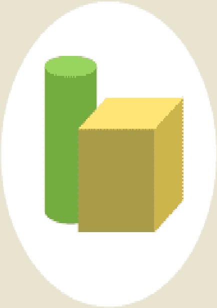
Temperature



Luster

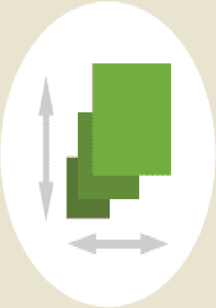
Hardness

Extensive Properties



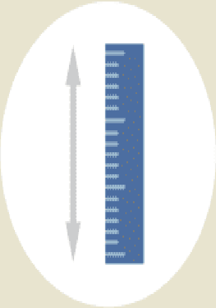
Volume

Mass



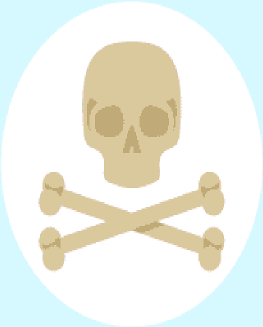
Size

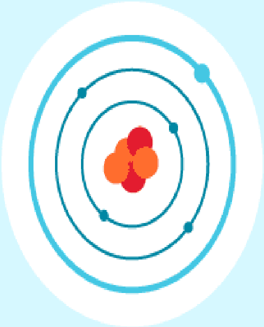
Weight

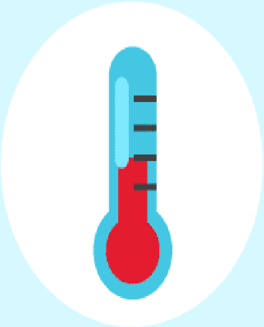


Length

Chemical Properties

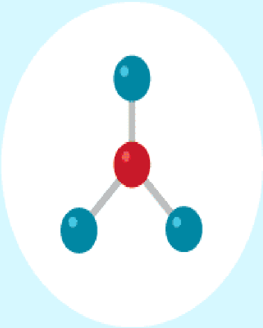

Toxicity

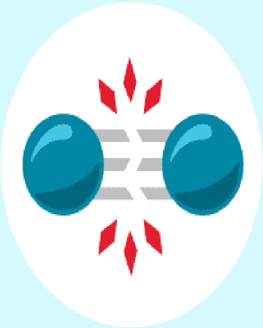

Oxidation States

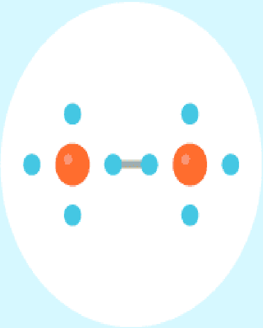

Heat of Combustion

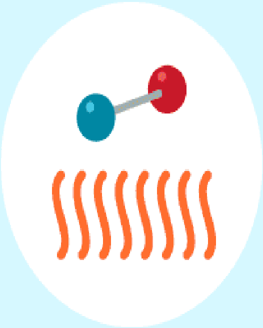

Chemical Stability


Flammability


Coordination Number


Reactivity


Possible Chemical Bonds


Enthalpy of Formation

- **Additive Properties** are due to addition of individual property of each atom or individual functional group present in that material.

  Example: Molecular weight or mass of a substance

- **Constitutive Properties** are dependent on the arrangement of atoms and bonds in its structure.

  Example: Optical activity or rotation, surface tension and viscosity.

- **Additive and Constitutive Properties** are due to both, the type of atoms present in it and their intramolecular arrangement.

  Example: Molar refraction, surface tension and viscosity.

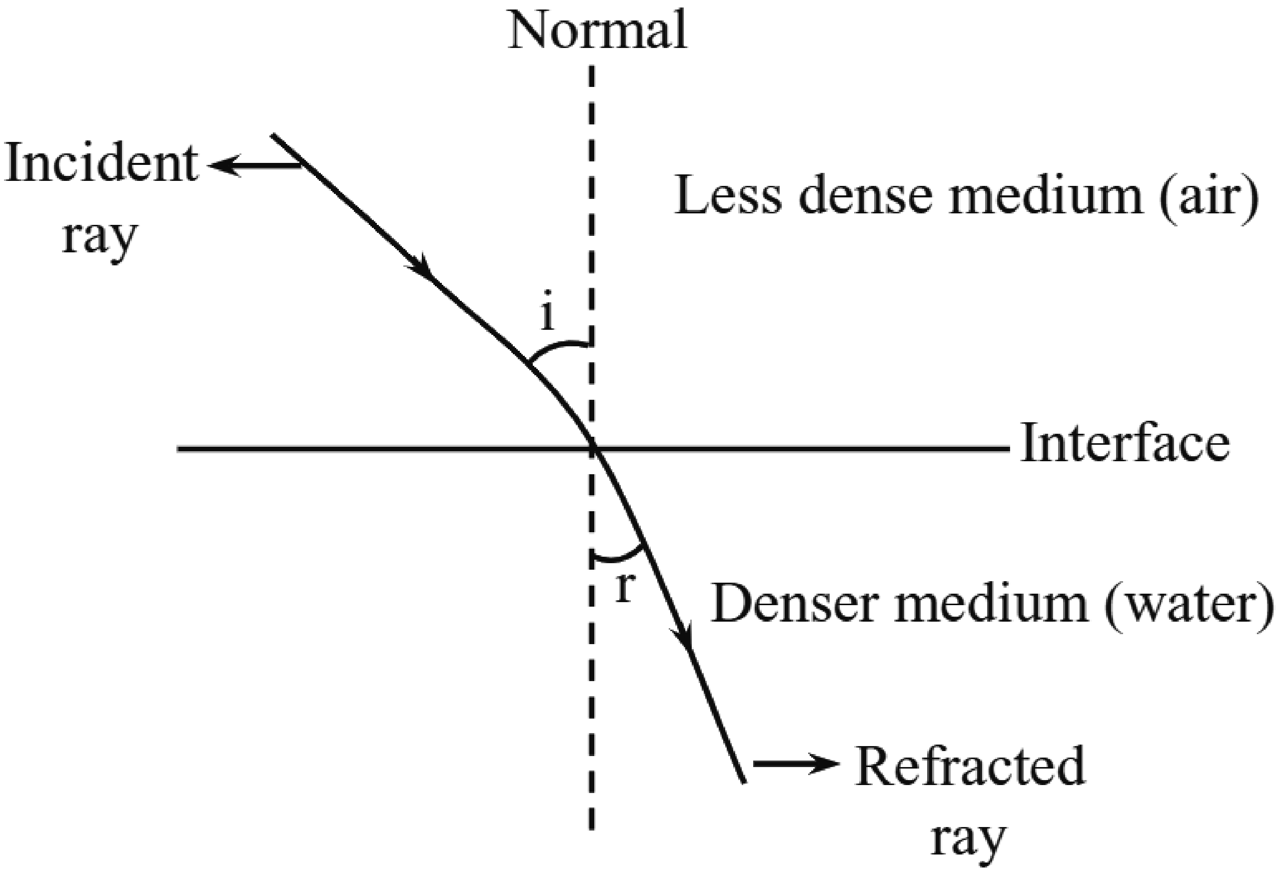
- **Colligative properties** are those which depend upon number of basic constituents like atom, molecule or particles present in the solution.

  Example: Freezing point depression, boiling point elevation, vapor pressure and osmotic pressure.

Property	Base	Example
Additive Property	Addition of individual property of each atom or individual functional group present in that material	Molecular weight or mass of a substance
Constitutive Property	Arrangement of atoms and bonds in its structure	Optical activity or rotation, surface tension and viscosity
Additive and Constitutive Property	Both, the type of atoms present in it and their intramolecular arrangement	Molar refraction, surface tension and viscosity
Colligative Property	Number of basic constituents like atom, molecule or particles present in the solution	Freezing point depression, boiling point elevation, vapor pressure and osmotic pressure

REFRACTIVE INDEX

- A Dutch physicist called Willebrord Snell in year 1621 gave relationship between angles when light passes from one medium to another medium.
- A beam of light when allowed to pass from one medium to another, it changes its direction.
- When a beam of light is permitted to pass from a less dense medium like air to denser medium like water the light ray turns towards the normal plane. Similarly, when a beam of light is permitted to pass from a denser medium to a less denser medium, the light ray turns away from the normal plane, this phenomenon in change in direction of light is termed as refraction.
- Refractive index (RI) is defined as ratio of velocity light in any selected medium to the velocity of light in vacuum or air.



- Mathematically it can be represented as follows;

$$n = \frac{\text{Velocity of light in selected material}}{\text{Velocity of light in vacuum or air}} = \frac{c}{v}$$

- Refractive index is a unitless and dimensionless quantity.
- Snell's law can also be used to describe refractive index. This law states that refractive index is ratio of sin of angle of incidence (i) to the sin of angle of refraction (r).

$$n = \frac{\sin \mathrm{i}}{\sin \mathrm{r}}$$

- Refractive index is a distinctive property of a liquid. Refractive index depends upon wavelength of light used and temperature.
- In general, refractive index is denoted as $[n]_{\mathrm{D}}^{20}$.

Where,

20 = Temperature at which refractive index has been determined (°C)

D = Line emission of sodium at 589 nm

- Refractive index of most of substances is more than air; because the majority of material is denser than air hence speed of light in air is more than reference substance. Below table shows refractive index of some of material.

Medium	**Refractive index**
Air	1
Water	1.330
Ethyl Alcohol	1.36
Acetone	1.36
Diamond	2.417
Glass	1.52

MEASUREMENT of REFRACTIVE INDEX

- Refractive index can be measured by using instrument called as refractometer. Different types of refractometer like Abbes refractometer, Pulfrich refractometer, Immersion refractometer are used for determination of refractive index.
- The most common, laboratory scale refractometer is Abbes refractometer. Abbes refractometer has several advantages as follows;

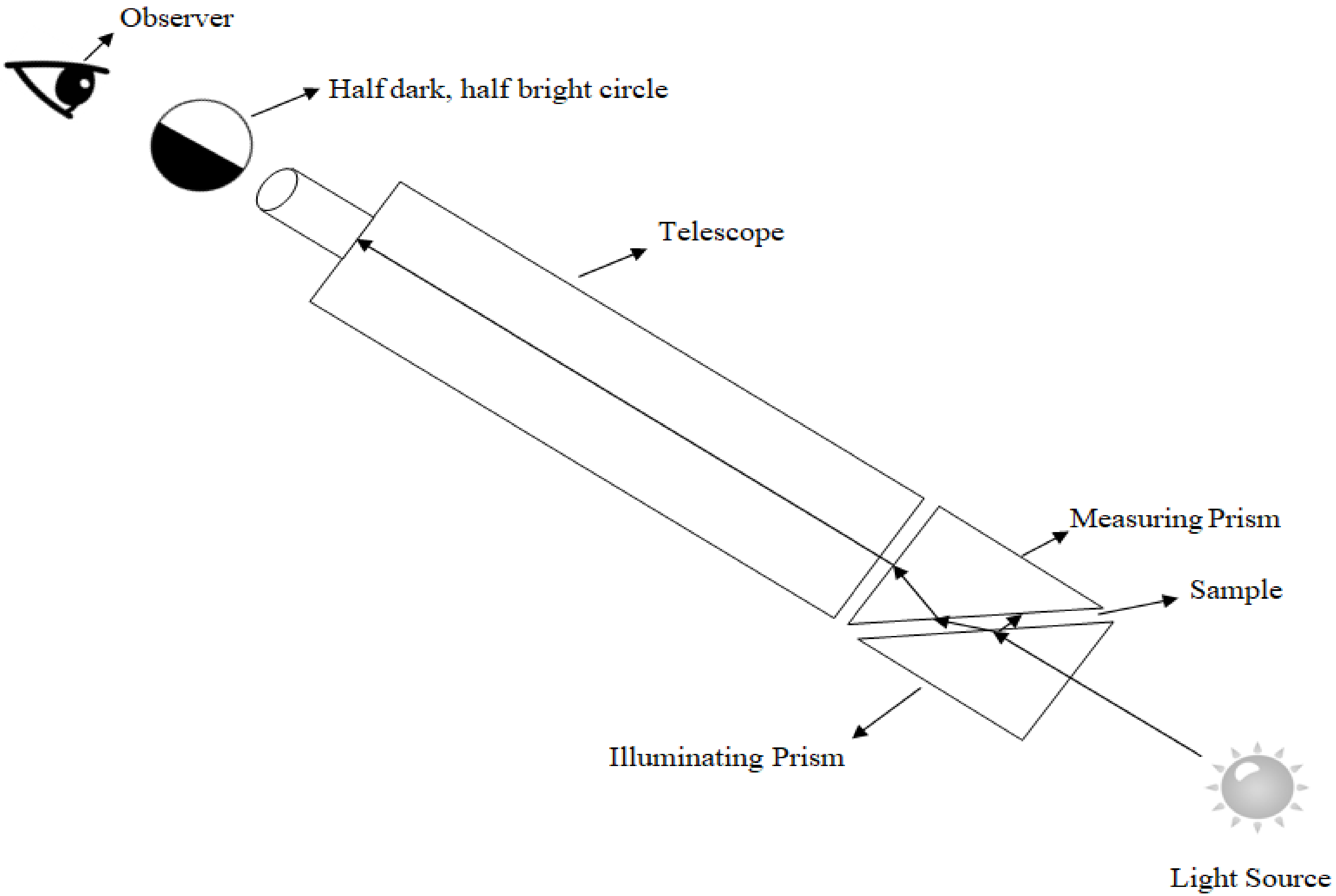
  - It is very compact hence require very less space and easy handling.

  - Very small sample is required.

  - Can be used to determine refractive index of large number of material.

  - Ordinary light can also be used for determination of refractive index.

- The schematic representation of Abbes refractometer is shown in figure -



- **CONSTRUCTION OF ABBES REFRACTOMETER:**

Abbes refractometer consists of the following parts:

1. Telescope:

Telescope is used to observe changes in the direction of light rays.

2. Prism Assembly

It consists of two prisms mainly illuminating prism and measuring prism. These two prisms are separable to place sample in between them as a very thin film.

3. Scale

Scale is used for calibration of refractometer. Also it is used for measurement of refractive index of sample.

4. Adjusting screw:

Adjusting screw is used for adjusting light such that half black and half bright circle is observed so that accurate reading can be obtained.

- **WORKING OF ABBES REFRACTOMETER:**

- The sample whose refractive index is to be measured is placed between the two prisms as a thin film.

- Light is allowed to enter from lower side of refracting prism.

- When viewed through the telescope, either dark band or light band or combination of light and dark band is observed.

- The adjusting screw is then slowly rotated, such that circle becomes half dark and half bright. When half dark and half bright band is observed, reading is recorded.

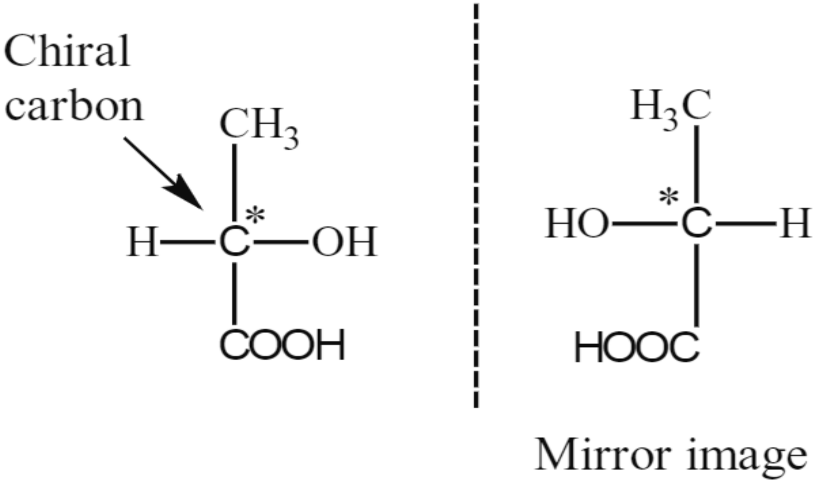
APPLICATIONS of REFRACTIVE INDEX

- The major application of refractive index is to determine the purity of sample.
- Measurement of refractive index helps in determining the concentration of the solute present in a solution.
- It helps in identifying a compound.
- It helps to determine the purity of a substance.
- It is used to determine the molar refractions of a compound which in turn provides useful information regarding its structure.
- Refractive index can also be used for determination of molecular weights and structure of organic compounds.
- Refractive index is used to measure refraction characteristics of solid, liquid and gases.

OPTICAL ACTIVITY

- An ordinary light consists of electromagnetic waves having oscillation propagating in all directions called as unpolarized light.
- When such light is passed through polarizer like Nicol prism it gets converted into light which have oscillations propagating in only one direction. Such light is called as plane polarized light.
- When any compound rotates plane polarized light passed through it through some angle, such compound is called as optically active compound.
- This property of optically active substance is called as **optical rotation** and angle through which light is rotated is called as angle of rotation.

- Optically active compounds are those who has carbon atom in centre attached to four different groups. Such carbon atom is called as chiral carbon.
- Chiral atom is required for a molecule to show optical activity. A chiral molecule is not superimposable on its mirror image and does not have plane of symmetry.
- For example in lactic acid central carbon atom is attached to four different groups like CH_3, H, OH and COOH.
- The two isomers which are not mirror images of each other are termed as enantiomers.



- Based upon which direction plane polarized light is rotated by optically active compound it can be classified into following two types,
- When the substance turns the plane polarized light towards right side or clockwise, it is called dextrorotatory and is denoted by (+) or (*d*).
- When the substance rotates the plane polarized light towards left side or anti-clockwise, it is called levorotatory and is denoted by (–) or (*l*).
- Optical rotation of a substance depends upon the wavelength of light, temperature and density of an optically active substance. It is an intrinsic property of an optically active compound.

- **Specific rotation:**
- Specific rotation is characteristic constant value for given compound.
- Specific rotation is defined as rotation produced when plane polarized light is passed through one decimeter (10 cm) length of sample solution having concentration of 1 gm / ml at specific temperature.
- Following formula is used for description of specific optical rotation.

$$\text{Specific rotation} = [\alpha]_{\lambda}^{t} = \frac{\alpha}{l * c}$$

Where,

t = Temperature at which optical rotation is measured.

λ = Wavelength of light used

α = Observed rotation

l = Path length

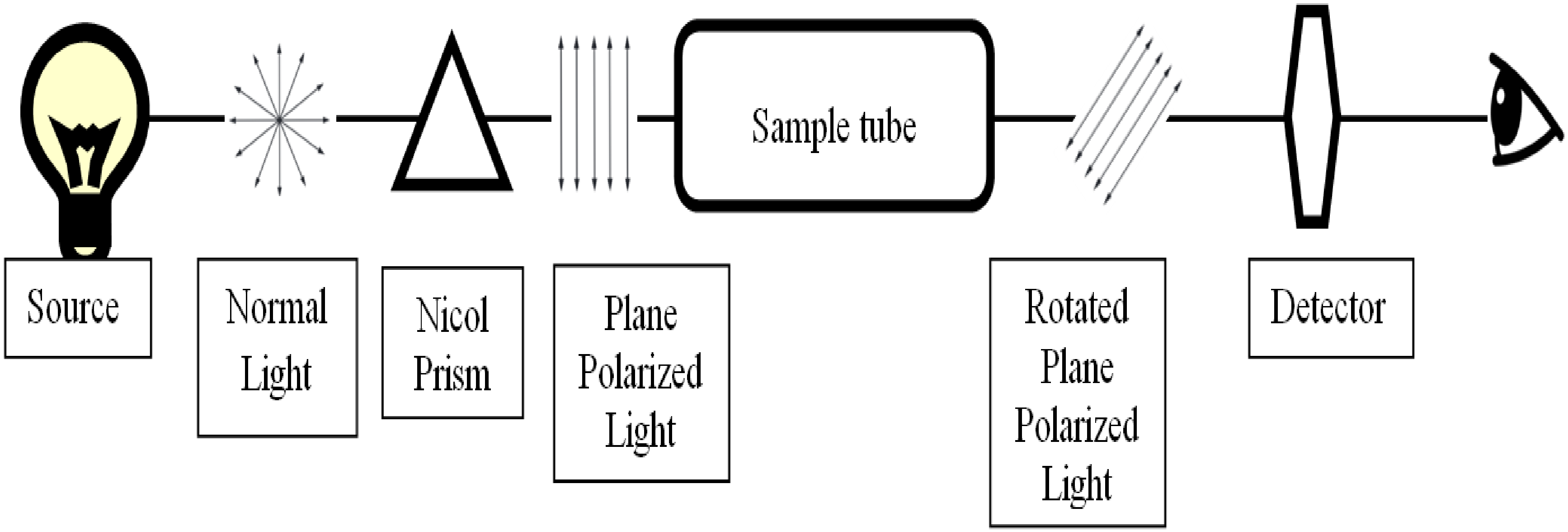
c = Concentration in grams/liter

- **SPECIFIC ROTATION:**
- Sodium D line is used as source of light in instruments which have wavelength of 589 nm.
- While writing specific optical rotation, solvent and concentration is mentioned in bracket. For example optical rotation of glucose can be written as,

$$[\alpha]_D^{30} = \pm 52.7 \text{ (water, concentration: 0.5 gm/ml)}$$

- In above example D represent Sodium D lamp as a source, 30 represent temperature 30 °C. ±52.7 represent optical rotation of dextro and levo rotatory glucose mixture. Water is a solvent with 0.5 gm/ml concentration of glucose in it.

MEASUREMENT of OPTICAL ACTIVITY



- **CONSTRUCTION OF POLARIMETER:**

A polarimeter consists of the following components.

Source of Light

Sodium vapor lamp (D-line source) is used as the source of light.

Polarizer

Nicol prism or polaroid lens is used as a polarizer. It converts ordinary beam of light into plane polarized light.

Sample Tube:

It is used for holding the optically active substance whose optical rotation is to be measured. Liquid substance can be directly added to the sample tube. For solids, precisely weighed quantity is initially dissolved in water or other suitable solvent and then filled in the sample tube.

Analyzer/ Detector:

It is used for making circle half dark and half bright during the measurement of optical rotation. It can be rotated and is connected to a scale which helps in reading the angle of rotation.

- **WORKING OF POLARIMETER:**

  - The substance whose optical activity is to be measured is added to the sample tube.

  - The optically active compound rotates the plane of polarized light. The extent of rotation is read from the scale, while the direction of rotation is noted.

  - Any change in the direction of rotation of plane polarized light with only the solvent is determined and the extent of rotation is read from the scale.

  - Difference in the readings obtained with and without sample gives the angle of rotation. This value is substituted in the formula to determine specific rotation of the substance.

APPLICATIONS

- Specific rotation helps in determining identification of compound.
- It helps in determining the purity of the substance.
- It also helps in quantitative analysis i.e., in determining the concentration of solute in a solute.
- To study rate of reaction in chemical kinetics.
- For determination of adulterants.

DIELECTRIC CONSTANT

- The ability of a system to store an electric charge is called as capacitance.
- Capacitance is dependent upon the type of medium in between the parallel plates called as dielectric medium and distance in between them.
- Ratio between the electric charges on the two parallel plates to the potential difference between the plates is called as Capacitance (C).

$$C = \frac{q}{v}$$

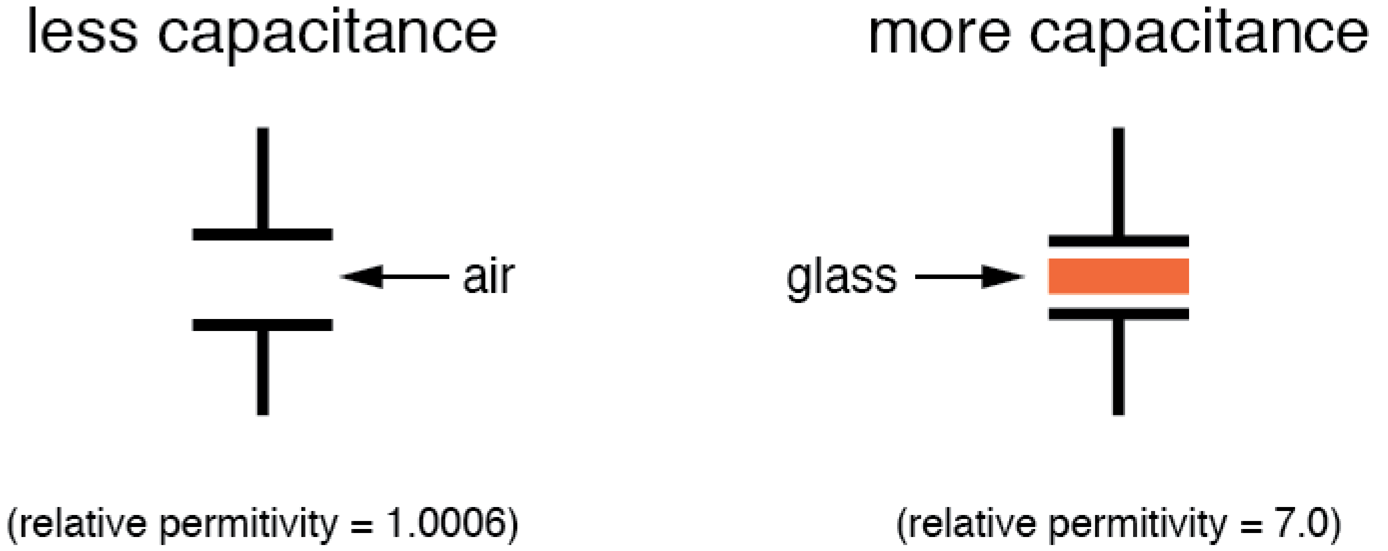
Where,

C = Capacitance

q = Electric charge

v = Potential difference

- The capacitance of condenser is dependent upon thickness of condenser separating the plates. C_0 is the capacitance of reference medium which is vacuum.

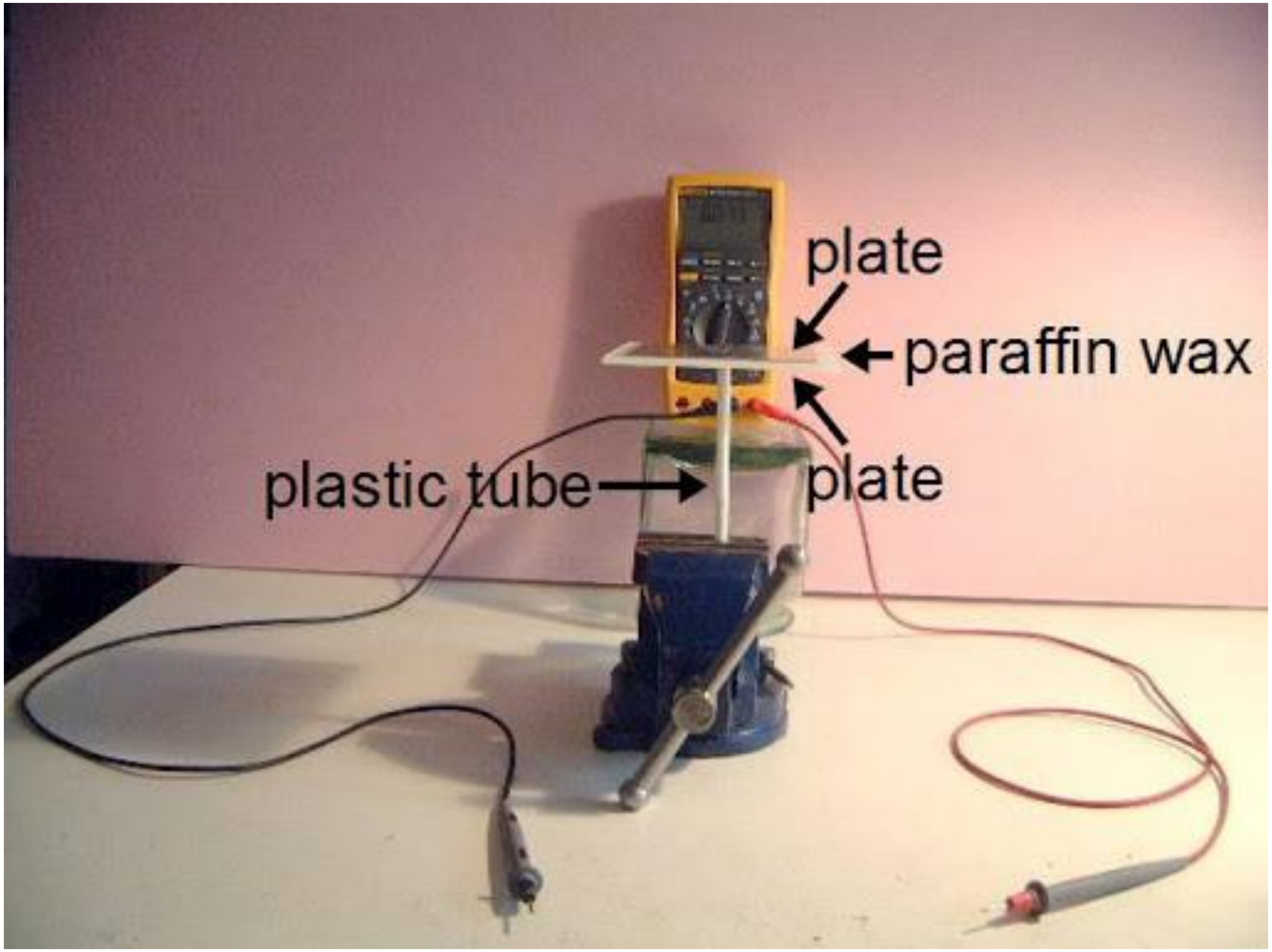


- **Dielectric constant (ε)** is defined as ratio of capacitance of the medium C_X to the capacitance of the vacuum.

$$\varepsilon = \frac{C_X}{C_0}$$

- As it is ratio, dielectric constant has no unit.
- Dielectric constant also called as relative permittivity of a solvent is measure of magnitude of charge separation within molecule i.e. polarity.
- Higher dielectric constant of molecule indicates high polarity means high charge separation within the molecule.

MEASUREMENT



Components:
Plates, Electrodes, Insulating Material, Recorder

dielectric constant: 1

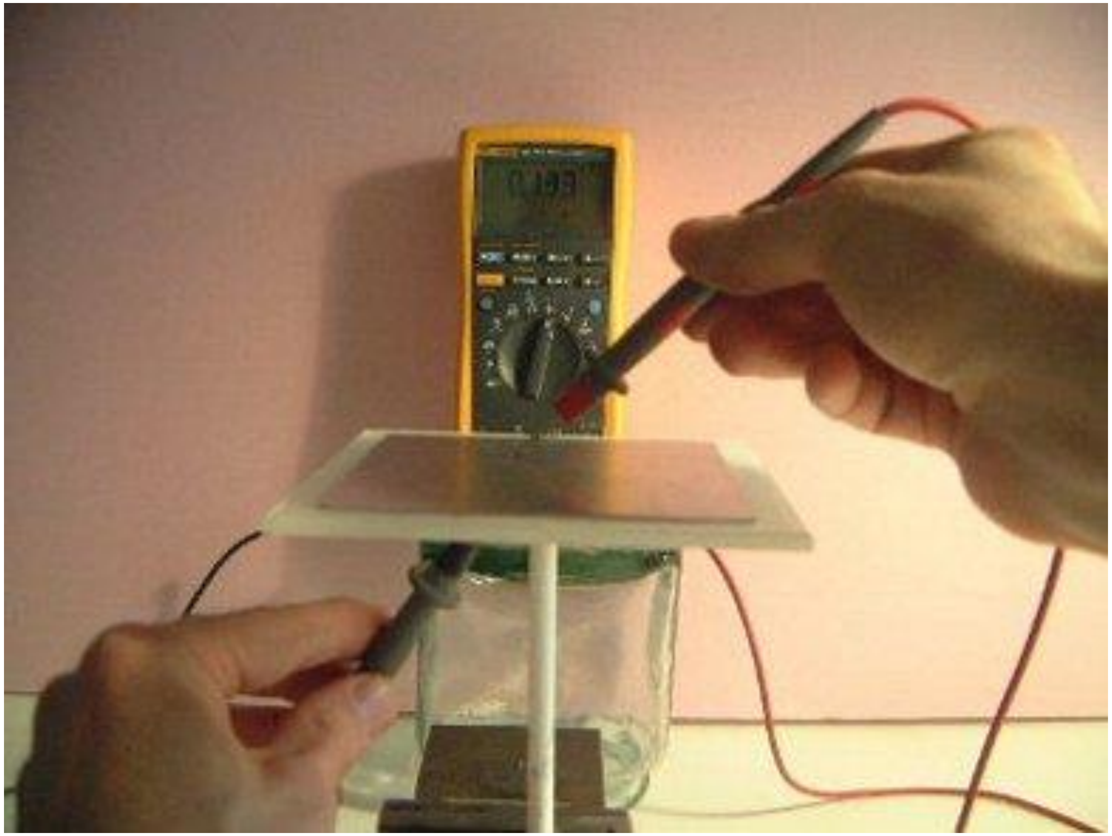
capacitance: ↓

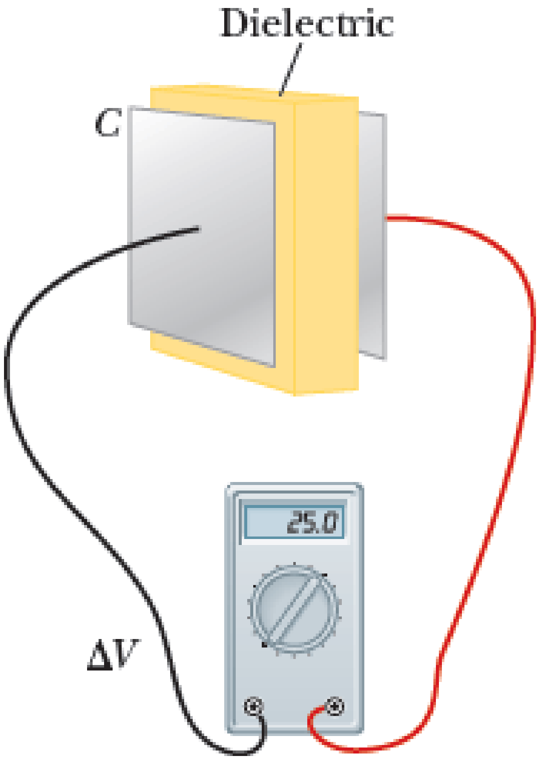
dielectric constant: 2.2

capacitance: ↑

- **WORKING :**

Step 1: measure the capacitance of the wax capacitor

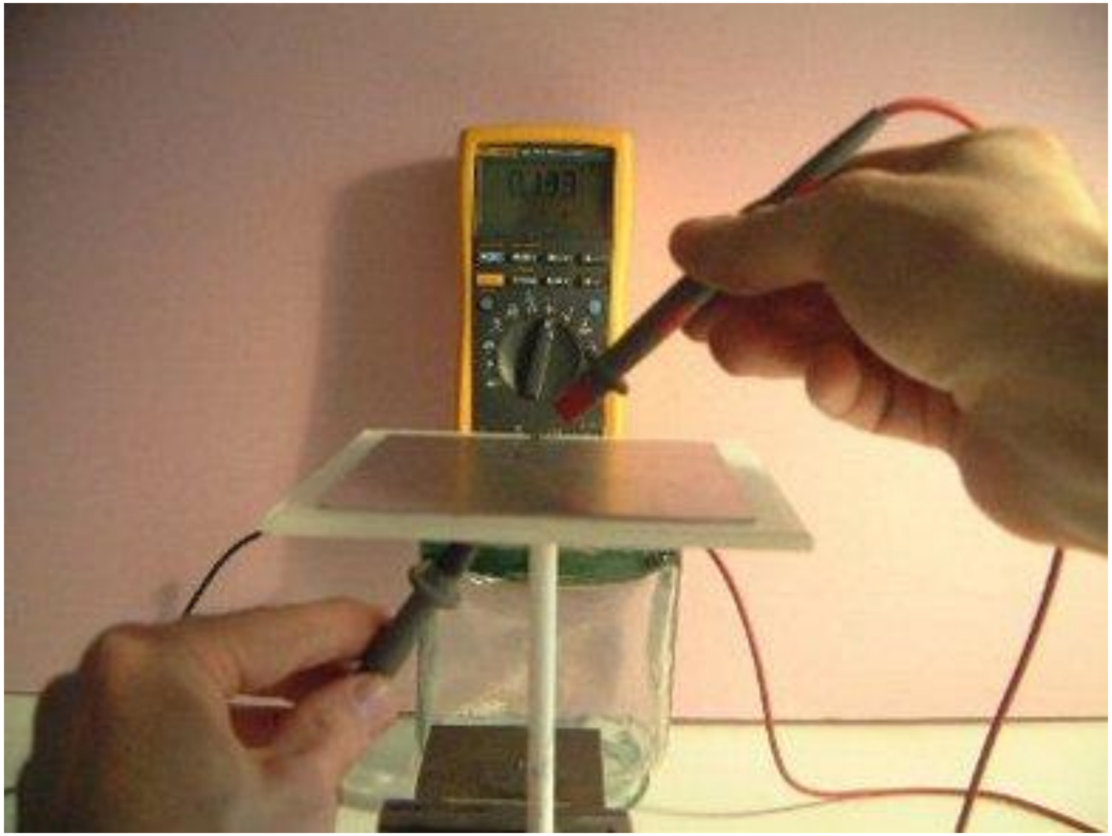


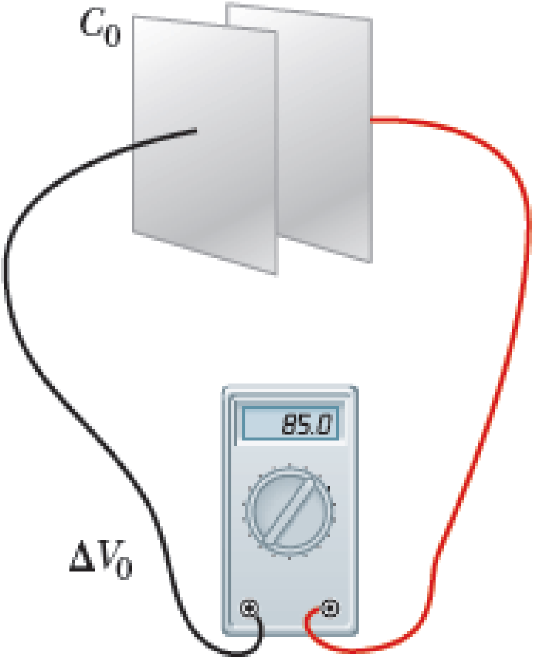


First measure the capacitance of the wax capacitor, shown in the diagrams. A 4mm thick, square piece of wax is prepared. For the plates, lets cut some square pieces of aluminum flashing which, when placed on the wax, don’t quite cover all of the wax surface. Now one plate is hot glued to the top of a plastic tube to suspend it in the air. Then build a capacitor sandwich by placing wax on the first place, then the other plate on top of the wax. As you usually do when measuring capacitance, before making the measurement use the meter’s REL function to store the capacitance of just the probes themselves. That zeros out the meter. Then measure the capacitance of the plates and wax capacitor. We get 0.053nF, which is my **Cm**.

- **WORKING :**

Step 2: measure the capacitance of the air capacitor





Next up is to measure the capacitance of the air capacitor, shown in the above diagram. One plate is hot glued to another plastic tube and arrange the plates 4mm apart with only air between them, making sure the spacing is the same as when the wax was between the plates. That creates the same capacitor with the only difference being the use of air as the dielectric. We get a capacitance of 0.024nF, which is my **Ca**.

Doing the calculation, the capacitance with the wax (**Cm**), 0.053nF, divided by the capacitance with air (**Ca**), 0.024nF, we can get a dielectric constant of 2.2. Note that it’s dimensionless since it’s a ratio of two values that have the same dimensions.

APPLICATIONS

- Dielectric constant is used to determine the polarity of solvents.
- Depending upon the values of dielectric constant the solvents can be arranged accordingly which is helpful to choose the appropriate solvent with desired polarity.
- Drug solubility can be increased by choosing suitable solvent or solvent mixture depending upon dielectric constant.

DISSOCIATION CONSTANT

- Dissociation is a process by which chemical compound break down into smaller constituents.
- Most of the drugs are either weak acidic or weak basic. These drugs may undergo process of dissociation. Dissociation may occur in solid, liquid or gaseous state. $A_x B_y \rightleftharpoons xA + yB$
- Dissociation of a drug molecule A_xB_y undergoing can be given as follows;

Dissociation constant is defined as tendency of particular substance in solution to be dissociated into ions. It is equal to the product of respective ion concentration divided by the concentration of non-ionic molecule.

Dissociation constant (pK_a) can be written as

$$pK_a = \frac{[A]^x[B]^y}{[A_xB_y]}$$

Where,
[A] is molar concentration of A
[B] is molar concentration of B
$[A_xB_y]$ is molar concentration of A_xB_y.

- Degree of dissociation determines the relative amounts of ionized and unionized forms of the drug and influences the distribution of mainly weakly acidic or weakly basic drugs.
- The ratio of ionized and unionized drugs is given by Henderson-Hasselbalch equation.

$$\mathrm{pH} = \mathrm{p}K_a + \log \frac{[\text{Unionized form}]}{[\text{ionized form}]}$$

- The above Henderson - Hasselbalch equation aids in calculating the ionization constant of compounds at a particular pH.

MEASUREMENT

Dissociation constant is measured by using following methods:

Potentiometric titration

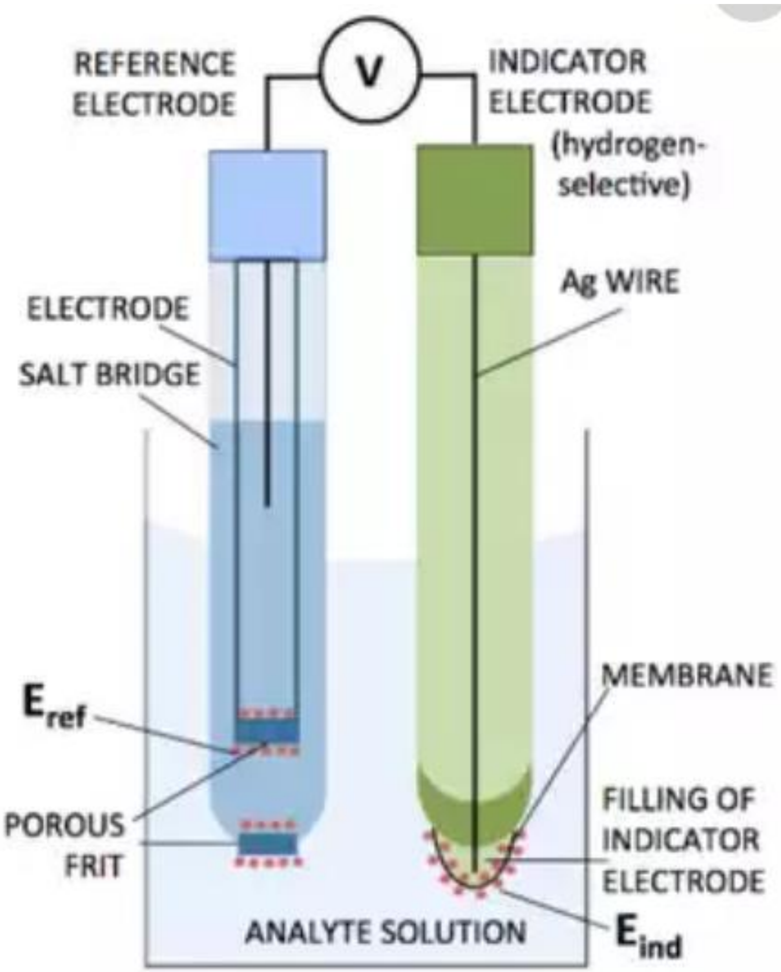
Spectrophotometric method

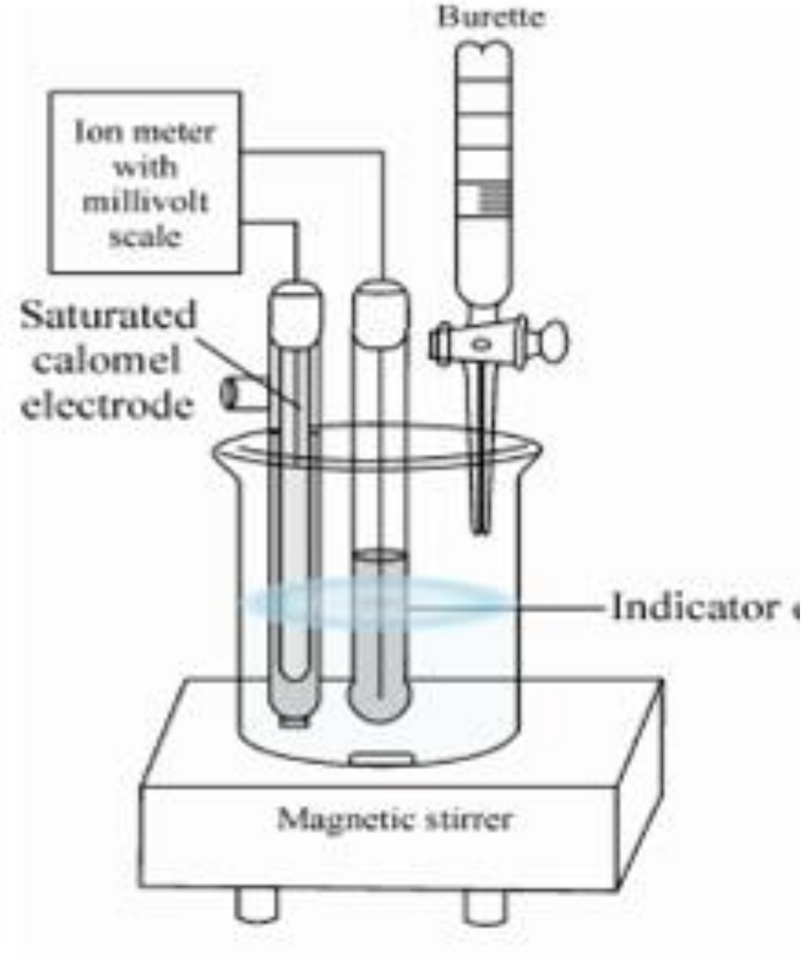
Calorimetry Method

Liquid Chromatography

Capillary Zone electrophoresis

POTENTIOMETRIC TITRATION





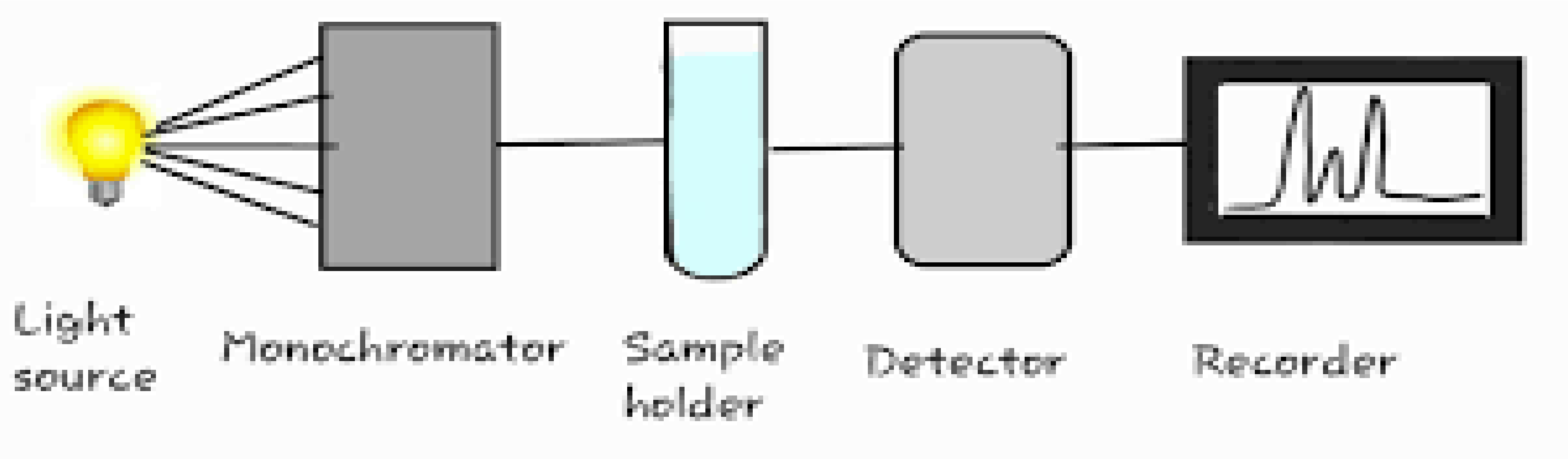
$$E_{\text{Cell}} = E_{\text{ref}} + E_{\text{indicator}} + E_{\text{junction}}$$

Dissociation of a week acid represents one of the proton exchange reaction; they are also called as acid-base reactions. According to the Bronsted-Lowry classification, an acid is a proton donor (protogenic substance) and a base is a proton acceptor (protofilic substance). In a potentiometric titration, a sample is titrated with acid or base using a pH electrode to monitor the course of titration. The pKa value is calculated from the change in shape of the titration curve compared with that of blank titration without a sample present. Potentiometric titration is based on the quantitative relationship of the E.M.F. of a cell as given by the following equation.

$$E_{\text{Cell}} = E_{\text{ref}} + E_{\text{indicator}} + E_{\text{junction}}$$

SPECTROPHOTOMETRIC METHOD

Component and working of UV-Visible spectrometer



The Principle of UV-Visible Spectroscopy is based on the absorption of ultraviolet light or visible light by chemical compounds, which results in the production of distinct spectra.

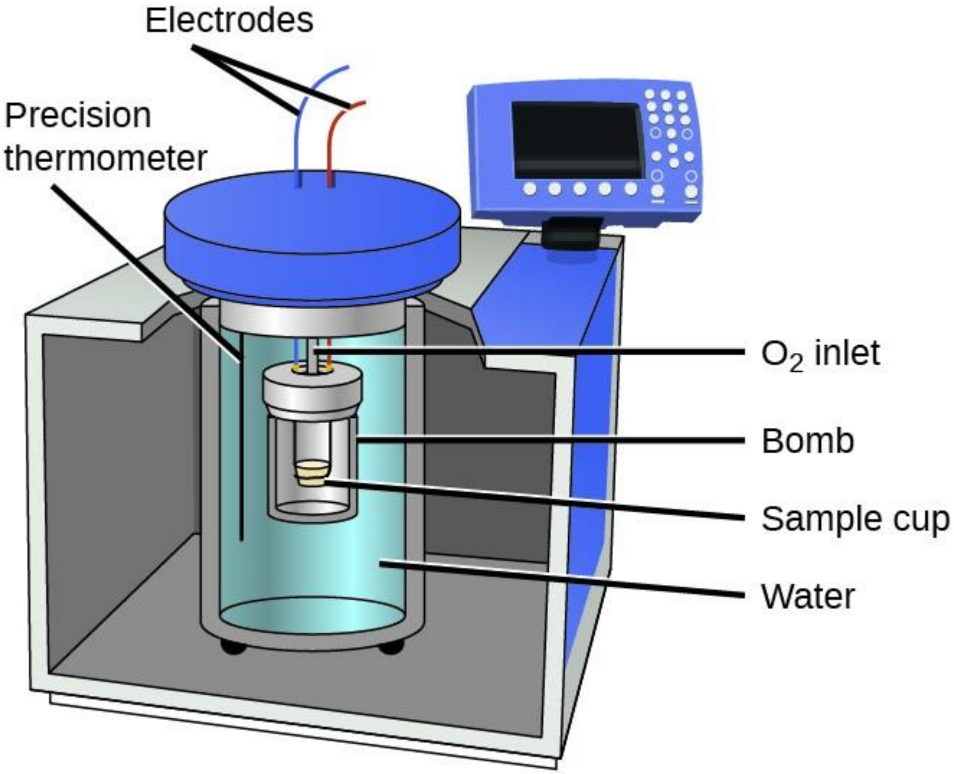
Component and working of UV-Visible spectrometer

- **Light source -** To cover the entire UV and Visible range a deuterium lamp for the 190 to 400 nm part of the UV spectrum, and a tungsten lamp 400 to 800 nm for the visible part.
- **Monochromator** – It works with purpose to resolve polychromatic radiation into individual wavelengths. It consists of an entrance slit to accommodate the source radiation and mirrors to pass the light through the system.
- **Prism -** It reflects light at the surface of two interfaces creating angular dispersion. The degree of dispersion depends upon the optical angle of the prism.
- **Grating -** When light transmits through or reflects off a grating, the grooves cause the light to diffract, dispersing the light into its component wavelengths.
- **Detector -** The purpose of a detector is convert radiant energy received into an electrical signal which can be multiplied and measured as a flowing current.

UV-Visible spectroscopy is based on the principle of the absorption of electromagnetic radiation from the 200–800 nm range and following excitation of electrons to higher energy states. UV–VIS spectrophotometry handles compounds with lower solubility and lower sample concentrations. A number of aromatic molecules are easily determined by UV spectroscopy. The λmax of two different form of drug must be different. There are various UV spectroscopic methods such as Simultaneous equation method, 96 well microtiter plates method , Multipeaks Gaussian fitting method, Molar ratio method, Least squares nonlinear regression of Multi-wavelength spectroscopic method, Second derivative method, Orthogonal method, are used to dissociation constant.

CALORIMETRY METHOD

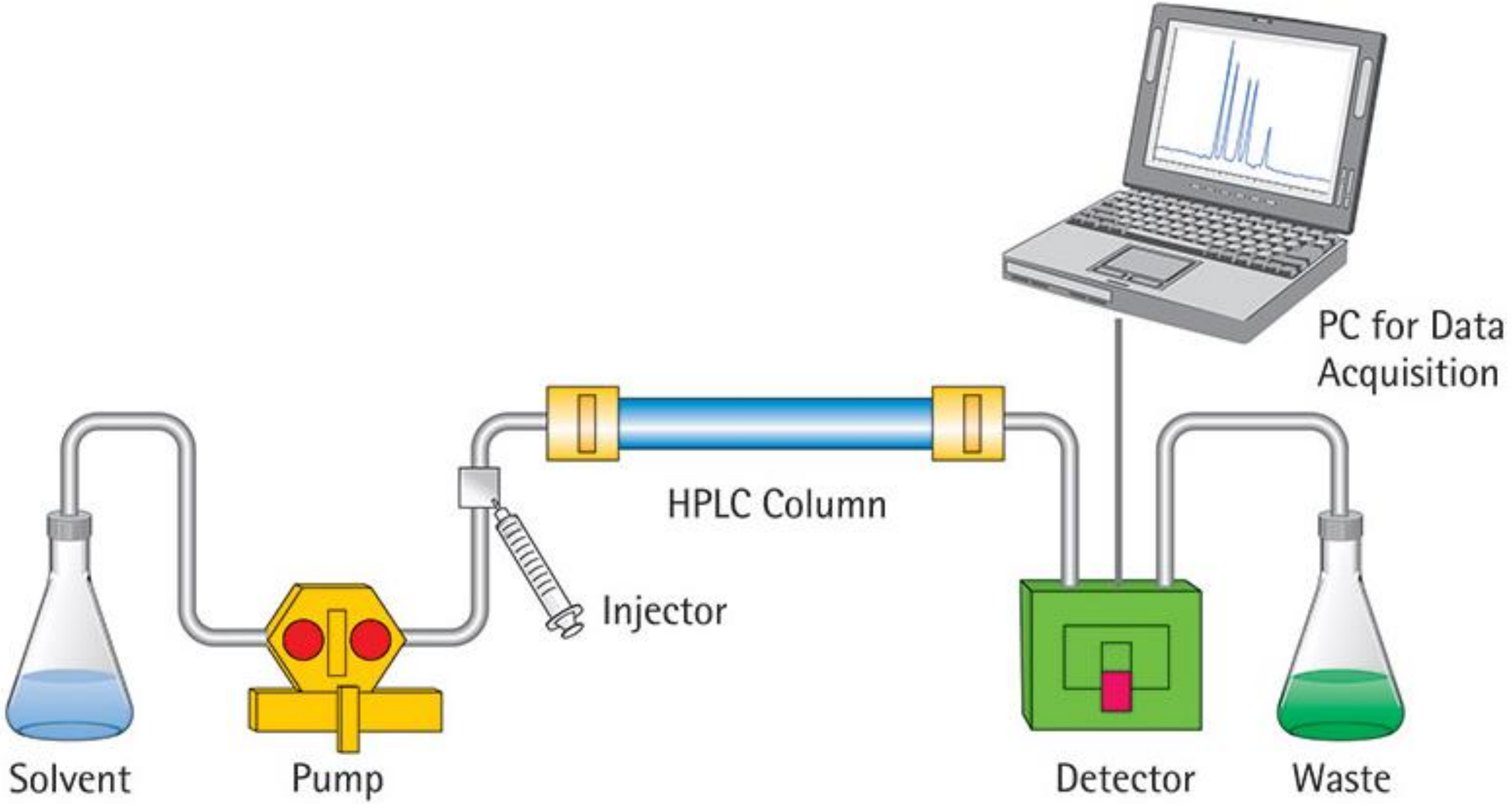
(a)



(b)

All calorimetric methods work by the same principle of measurement of the amount of heat evolved as a physical or chemical process takes place in a sample. For the measurement of pKa values, in Isothermal Titration Calorimetry [ITC], a regular acid-base titration is carried inside the calorimeter while the energy required to keep the temperature constant is measured. This method also calculates the pKa indirectly from a measured enthalpy change ΔH. By plotting the minima or maxima versus pH, a sigmoid curve is obtained from which the pKa can be determined from the inflection point.

LIQUID CHROMATOGRAPHY



The separation principle of HPLC is based on the distribution of the analyte (sample) between a mobile phase (eluent) and a stationary phase (packing material of the column).

Component and working of HPLC

- **The Pump -** generates a flow of eluent from the solvent reservoir into the system
- **Injector -** The simplest method is to use a syringe, and the sample is introduced to the flow of eluent.
- **Column -** The separation is performed inside the column. The recent columns are often prepared in a stainless steel housing, instead of glass columns. The packing material generally used is silica or polymer gels compared to calcium carbonate.
- **Detector –** A detector is used to observe the obtained separation.
- **Recorder -** Nowadays, a computer-based data processor (integrator) is more common.
- **Degasser -** Degasser uses special polymer membrane tubing to remove gases.
- **Column Heater -** To keep consistent temperature conditions.

The different retention behavior of the protonized and the nonprotonized form of the test material serves the base for liquid chromatography method. The retention time is determined in relationship to the pH-value of the mobile phase by reversed - phase HPLC. The high performance liquid chromatography method is advantageous to determine pKa value of low water soluble drug with low sample consumption, rapid sample analysis, high sensitivity and precision. The most important feature is the excellent resolution that can be achieved under a wide range of conditions for very closely related molecules, as well as structurally relatively distinct molecules. Dissociation constant is greatly affected by changing in pH, ionic strength, and temperature. The pH of the mobile phase affects retention of acidic and basic drug.

- A general equation which relates the observed retention factor to the pH of the mobile phase, the dissociation constants, and the retention factors of the different ionic species has been used to determine dissociation constant of polyprotic weak acid and base. It is written as:

$$K_D = K_o + \frac{\sum_{r=1}^{n} K_r \,.\, K_a.[r]e^{rx}}{1 + \sum_{r=1}^{n} K_a.[r]e^{rx}}$$

Where,

Ko retention factor of undissociated species

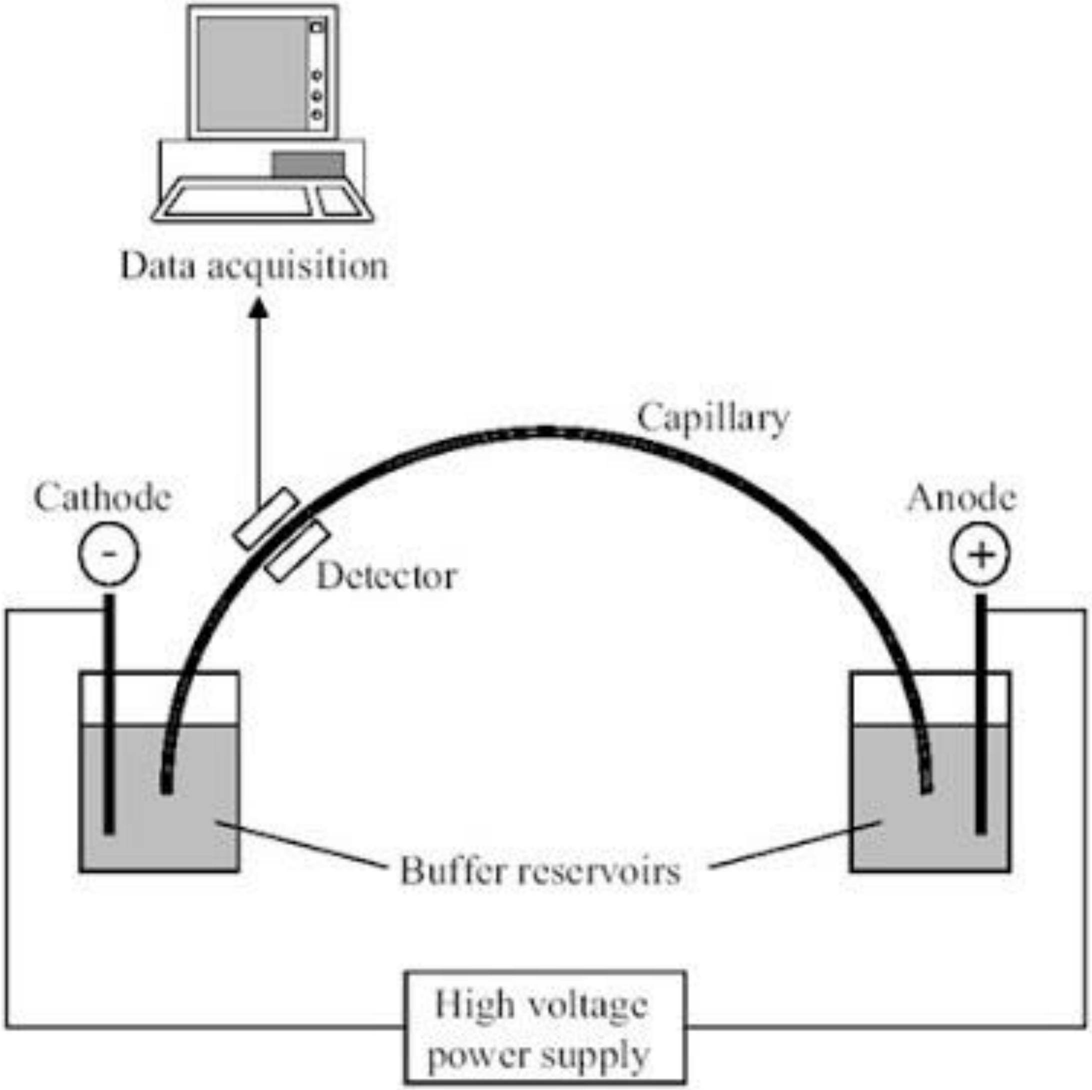
Kr value is the retention factor of dissociated species

Ka[r], product of the first r- dissociation constants

n is the ionisation constant

X is related to pH of the mobile phase: x=2.303.pH

CAPILLARY ZONE ELECTROPHORESIS



Capillary zone electrophoresis [CZE] serves as a useful tool for determination of pKa values with several advantages over potentiometric and spectroscopic methods. Since the pH influences the electrophoretic behavior of the substances, a relation can be established between pH, pKa and the electrophoretic mobility of compounds. The electrophoretic mobilities were calculated using the following formula:

$$\mu_{ep} = \mu_{app} - \mu_{eof} = \frac{L_d - L_t}{V}\left[\frac{1}{t_m} - \frac{1}{t_o}\right]$$

Where,
μ_{ep} is the electrophoretic mobility of compounds in cm^2/Vs
μ_{app} is the apparent electrophoretic mobility of the solute in cm^2/Vs.
μ_{eof} is the electroosmotic mobility of a neutral marker in cm^2/Vs.
Ld is the distance from the injection point to the detector [cm]
Lt is the total length of capillary [cm]
V is the applied voltage [volt]
t_m and t_o are the migration times [s] of the analyte and neutral marker, respectively.

APPLICATIONS

- Dissociation constant is useful in determination of bioavailability of drug and distribution of drug inside body in tissues.
- Dissociation of drug also affects its solubility and permeation.
- Dissociation constant is also useful in pH indicators.
- Buffer design also depends upon dissociation constant.

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