

# 1. STATES OF MATTER

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## **Introduction**

*Matter is something that occupies space. It may be visible or invisible to human eye.*

*Whatever you take in this universe, it may contain fundamentally what we call as minute, atoms. The atom may, for convenience sake, be considered as primary matter or fundamental particle as it is electrically neutral, structurally complete and stable. When an atom is distinguished by its atomic number, it is termed as element. The name element is applied both to a single atom and to a group of similar atoms occurring as a mass. We have different elements in this universe. All the elements so far discovered have been named. Atomic number simply indicates the number of protons (or electrons) present in respective atoms. The classification of these elements is presented in, what we call as, Periodic table. So far, some 118 elements have been reported. However, only first 98 elements are said to be naturally occurring. Even within this 98 elements, 10 elements occur in traces. Further elements added to periodic table are only synthesized. Abundance in quantity is only with elements having lower atomic numbers.*

*An atom, therefore, consists of a positively charged nucleus (composed of protons and neutrons) with which orbital electrons (negatively charged) are associated. The number of orbital electrons is equal to the number of protons in the nucleus, and the number of protons in the nucleus defines the atomic number. The number of protons plus the number of neutrons is the mass number of the atom. Thus, most of the mass of the atom is concentrated in the nucleus. The density of the nucleus is quite unbelievable and is calculated to be  $2.4 \times 10^{14}$  g/ml. To appreciate this value, suppose, 1 ml of a substance is made of nuclei. This 1 ml of substance packed with protons would, then, weigh 250 million tons. The radius of an atom is approximately  $10^{-10}$  meter suggesting the atom is 100,000 times the size of nucleus. It means the electrons revolving around the nucleus would occupy a volume that is 100,000 times the volume of the nucleus. Therefore, the atom as a whole may be considered to be quite empty and yet, it is practically invisible.*

*Two or more, same or different, atoms combine (chemically) to yield a molecule when inter-atomic bonding occurs. There are small and big molecules. A small molecule is made up of two or more atoms. A big molecule, made up of many atoms, is called as macromolecule and it is considered to be of colloidal size which is also invisible but is detected in ultra-microscope and visible in an electron microscope. Thus, **a molecule is the smallest possible quantity of a substance**. New molecules are also formed in the laboratories and named.*

*(All the elements and the molecules and whatever is made of these elements and their molecules have been broadly classified in Vedas of India as **major five elements namely the earth (land), water, fire, air and ether**. The ether is only a part of **Space**. This classification is astonishing and it indicates the broad knowledge of impeccable acuity, as in the absence of any one of these five major elements, the life on earth is impossible.)*

*All elements **invariably** contain three main particles namely neutron (neutral), proton (positively charged) and electron (negatively charged). The element (or the atom) may have some other particles.*

*The nucleus was thought to consist of protons and neutrons; and to form an atom, only electrons needed to be added in external shells. Therefore, protons, neutrons, and electrons were considered as the elementary particles of atoms. In theory, all the elements in the periodic table can be made by splitting neutrons into protons and electrons, and by combining these particles in proper ratios. The nuclear physics has been progressively probing the atoms from the periphery to their center. The search for ultimate units of nuclear structure, by means of experiments, has revealed a spectrum of over 100 species, most of them unstable. The proton is no longer considered as ultimate particle, but is believed to be made up of particles called quarks. Whether these and other elementary particles are all composed of yet simpler elements remains to be investigated. Thus, the search for the ultimate units (same kind of particles) of nuclear structure or simply the atom has been a continuous effort from a long time back.*

*Professor Dr.C.Ramasamy who is my father, is of the opinion that there must be only one fundamental as well as ultimate unit particle which may constitute or contribute for the formation of all the elementary particles present in atoms of all the elements through some intermediate particle (or particles) formation involving some **unknown (or can never be known)** few steps involving /including enormous energy for their make-up in some unknown different ratios. The ultimate similar units or particles, contributing for the formation of all the atoms, must be the smallest with **no other particle smaller than this and naturally with no source for its existence**. It may be said that there exists no other particle smaller than this and hence, it must be the source for all. And it must exist by itself. This can never be seen or known or even thought of because the size is so minute of the minutest. Nor, can it be defined as a form of energy or matter. Therefore, it may be said that it virtually occupies nil space and has virtually no mass but at the same time occupying and filling the boundless Space in its invisible state. (As an analogy, we can imagine the air particles filling the atmosphere). It fills the Space and the Space is itself. It can only be assumed or believed. It must be many more thousand times smaller than Planck's length which is said to be  $1.6 \times 10^{-35}$  meter and is claimed to be the meaningful measure possible scientifically. However, the size of this particle is approximately given in Thirumandirum written by a Tamil saint or Siddhar by name Thirumoolar, Tamil Nadu, India, some thousands of years back as  $5.0 \times 10^{-41}$  meter and **he calls it as life particle**. For it, anything is possible by virtue of its size and*

*this size is mind boggling as the vastness of boundless Space. If we attempt to imagine the size of this particle, it will obscure or completely block our imagination (God really exists). What name can be assigned to this omnipotent, omnipresent, and omniscient **Conscious Particle** except the common noun, God? It is to be understood that no other particle is **conscious** except the “**life particle**” in this vast universe. As there can be no other particle except this, this must be the life particle or it is the life particle, existing in countless number becomes both the inanimate and animate beings. How wonderful it is, from such a particle, the universe(s) has evolved into boundless unimaginable diversifications including multi-coloured clouds, stars, planets, and galaxies that lie scattered throughout the space! And yet the space is one quarter of the Space as claimed by Vedas!]*

*Though the number of elements is comparatively very few, the number of molecules formed of them is unimaginably innumerable. It may be said that almost all the elements exist in combined form as molecules or compounds and to some extent as complexes which are said to be formed by the association of two or more interacting molecules or ions. The name compound may usually refer to a molecule with different atoms. New molecules or compounds and complexes are also being formed in the laboratories. The atoms or the molecules or complexes have properties of their own and we classify the properties as physical and chemical properties and if it is within the living system we call it as biological properties.*

*Atoms or molecules individually are themselves invisible. They may be seen if they occur as a mass. That is, if millions of atoms or molecules occur together as a mass, we can see it. For example, the element gold or silver or iron that we see consists of many million numbers of atoms even in its seeable smallest size. The same is true for molecules. For example, a small sugar particle may consist of millions of sugar molecules. The smallest size that can be seen by human eye is said to be around 40  $\mu\text{m}$ .  $1\mu\text{m} = 1/1000 \text{ mm}$  or  $1/10000 \text{ cm}$  (centimeter) but an atom is many million times smaller than this.*

*The atoms and molecules exhibit astonishing properties within a living system such as moving and non-moving living beings and that we study in biochemistry.*

*The atoms and molecules or simply the matter has mainly three states namely solid, liquid and gaseous states.*

*In the case of elements, the mercury alone is liquid and all other elements are either solids or gases. When molecules or compounds of atoms are considered, they occur abundantly in solid, liquid and gaseous states.*

**Different bonds formed between reacting atoms to form molecules**

We know all atoms have a nucleus, which accommodates protons and neutrons, and the electrons, which are constantly revolving around the nucleus. The attraction of a nucleus for electrons is termed its electro-negativity. Metals have low electro-negativity and hence, are termed as electropositive elements whereas non-metals (especially the halogens) have high electro-negativity and hence are called electronegative elements.

When two atoms with great electro-negativity difference react (i.e. one with electro-positivity and the other with electro-negativity), there is electron transfer and the bond formed between them is called the electrovalent or electrostatic bond. For example sodium chloride is formed of electrovalent bond.

When the two reacting atoms have similar electro-negativities such as two hydrogen atoms or two chlorine atoms, sharing of electrons between them takes place, each contributing one electron forming a bond. Such a bond is called covalent bond.

When the two atoms with less electro-negativity difference react, the atom with higher electro-negativity can also form covalent bond by sharing its electron with the electron of the other atom with lower electro-negativity. But in this case, the commonly shared electron pair is pulled closer to the atom with higher electro-negativity more strongly than the partner. This leads to polarization of molecule and a dipole results. Therefore, the process by which a dipole arises in a molecule is known as polarization. Such bonds are said to have partial ionic character. In general, a covalent bond is formed by the overlap of two atomic orbitals involved. With such formation of a bond among atoms, a molecule results. The bonding electrons are no longer restricted to their atomic orbitals. They, now, are free to move in a molecular orbital between the atoms in what is known as a ' $\sigma$ ' (sigma) molecular orbital.

It may be said that only the most electropositive atoms reacting with the most electronegative atoms form purely electrovalent bond (Ex. NaCl). Atoms with equal electro-negativities form purely covalent bonds (Ex.  $H_2$  or  $Cl_2$ ). The bonds formed from atoms between these extremes have partial covalent or partial electrovalent or ionic character (Ex. HCl or HF).

Atoms with orbital occupied by an unshared pair of electrons can share the electron pair (or donate both the electrons to) with an atom lacking two or more electrons in its valence shell. The bond thus formed is said to be a coordinate covalent bond. For example, the formation of ammonium ion ( $NH_4^+$ ) from ammonia ( $NH_3$ ) which has an unshared electron pair, and a hydrogen ion ( $H^+$ ), which has an empty 's' orbital (i.e. no electron pair), involves coordinate covalent bond.

**States of matter**

We know already that matter exists in three states namely solid, liquid and gas. Normally, we see the matter existing in these three states around us. There are some intermediate states also.

The two common factors, *the intensity of intermolecular forces* and the *temperature* strictly, determine the three states of matter.

### 1. Intermolecular forces between molecules

Atoms, ions and molecules have attractive as well as repulsive forces. In the absence of repulsive forces, attractive forces may tend to cause mutual destruction of molecules by interpenetrating and annihilating each other. Therefore, both attractive and repulsive forces operate between atoms, ions and molecules.

Solid and liquid molecules to exist as aggregates (or as a mass) or the solid and liquid states to exist, intermolecular forces must exist. An understanding of intermolecular forces is important in the study of physiochemical properties. Cohesion or attraction, between like molecules and adhesion or attraction, between unlike molecules are the manifestations of intermolecular forces. Gas molecules lack this coherence because of distance of separation between the molecules.

#### a) *Attractive forces*

Various attractive forces exist between molecules formed mainly of electrovalent and covalent bonds. The attractive forces may be due to ions, permanent dipoles, and induced dipoles interactions. Other type of bonds may also contribute for attractive forces.

Ions result from transfer of electrons from one atom to another atom. For example, sodium has 11 electrons and chlorine has 17 electrons and when they react between them, sodium transfers one electron to chlorine which accepts the electron forming an electrovalent bond between them as already mentioned. Thus the sodium becomes a positively charged ion and the chlorine becomes a negatively charged ion because of imbalance in the ratio of protons and electrons and the valency will dictate whether the ion is cation or anion. *Ion – ion interaction* is normally viewed from the standpoint of attractive force. Thus, a cation on one molecule will interact with an anion of another molecule giving rise to intermolecular association. This is the strongest force of all other attractive forces. There can be repulsive forces when like charged ions are brought nearer to one another.

Second type of attractive forces exists in covalent bonds. A covalent bond is formed as a result of sharing of electrons between atoms equally or unequally. In this, each atom contributes an electron to form a bond between them. Covalent bonds may be formed between same atoms or different atoms.

In the case of molecules formed of same elements (i.e. atoms) such as hydrogen, chlorine, oxygen, etc., there is an equal sharing of electrons to form their respective molecules  $H_2$ ,  $Cl_2$  and  $O_2$ . Such a bond formed between same elements is termed as a non-polar bond. In these molecules the dipole moment is zero. That means the molecule is electrically symmetrical.

In the case of atoms of different elements, the covalent bond is formed by unequal sharing of electrons, though both of them contribute one electron to be shared between them. This is due to the difference in the electron affinity between them. When a covalent bond is formed between them, the shared electron pair will always be displaced nearer to the more electrovalent atom. In this case, there is separation of charge and each atom will acquire a small charge i.e. one atom will have a positive charge and the other atom will acquire a negative charge. The separation of charges in these molecules such as hydrogen chloride, hydrogen fluoride, etc is permanent. As a result, these molecules give rise to a permanent dipole moment associated with the bond. Several such bonds within a molecule having many atoms may give rise to various bond moments and these bond moments contribute to overall value for the dipole moment of the molecule. Molecules having permanent dipole moment greater than zero are said to be polar molecules. Thus, if a molecule acts as if it has positive and negative poles i.e. if it has a partial separation of charge, it is called a dipole molecule or simply a **dipole**. Molecules with dipoles are said to be **polar or dipolar**. Such molecules are electrically unsymmetrical. An electrically symmetric molecule is designated as nonpolar. Polar (or dipolar) molecules often tend to align themselves with the surrounding molecules so that the positive pole of one molecule points toward the negative pole of other molecule. Thus, when polar molecules interact, it is termed as *permanent dipole – permanent dipole interaction or attraction or Keesom force*.

Ions can interact with a dipole molecule giving rise to ion-dipole interaction. Ions can also induce a dipole in nonpolar molecules and interact with them giving rise to *ion – induced dipole interaction*. When an ion or dipole molecule is brought close to a nonpolar molecule, the equally shared electron pair in the nonpolar molecule may get displaced towards the one or other atoms in the nonpolar molecules. This gives rise to an induced dipole moment in the bond of the nonpolar molecule. This is also termed as weak electrostatic force. The process by which dipoles arises is known as *polarization*. (This is something like an iron needle gets magnetized when it is in contact with a magnet). If the ion or polar molecule is withdrawn, the effect produced in the nonpolar molecule disappears. The interaction between a polar and nonpolar molecules results in *dipole – induced dipole attraction or Debye forces*. Even non-polar molecules induce mutually within themselves to give rise to induced dipole moment when they are brought close together and this is called *induced dipole – induced dipole interaction or London forces*. This dispersion or London force is sufficient to bring about the condensation of nonpolar gas molecules so as to form liquids and subsequently solids when molecules are brought quite close to one another.

Overall, ions, permanent dipole and induced dipole give rise to six types of attractive forces. They are:

- i) Ion – Ion attraction
- ii) Ion – permanent dipole attraction

- iii) Ion – induced dipole attraction
- iv) Permanent dipole – permanent dipole attraction (*Keesom forces*)
- v) Permanent dipole -- induced dipole attraction (*Debye interaction*)
- vi) Induced dipole-induced dipole attraction (*London forces*)

The last three types of attractions are, in general, known as *van der Waals forces* which relate to non-ionic interactions between molecules. Fig. 1.1

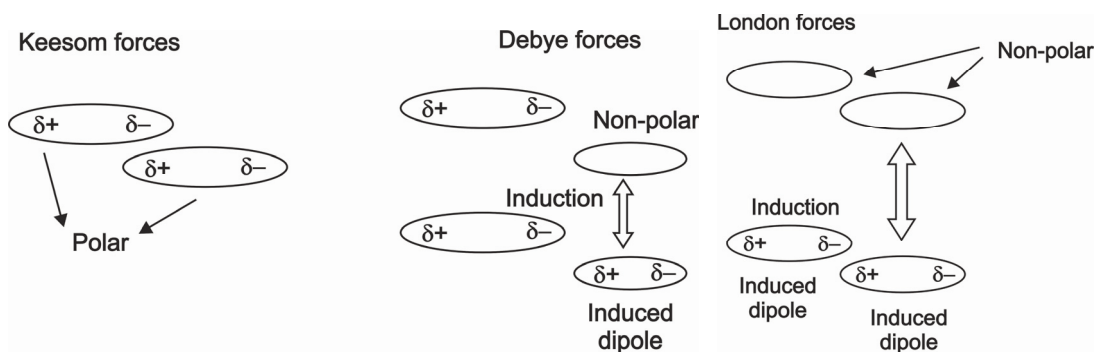
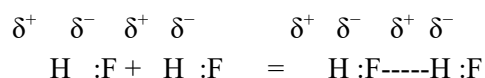


Fig. 1.1 van der Waals forces

There exists some weaker ion-ion interaction particularly in salt formation. Such weaker ion-ion interaction can be viewed as ion-ion interaction (in contrast to atomic ions interaction) from the standpoint of attractive forces. A cation on one molecule will interact with anion on another molecule giving rise to intermolecular association. Ion-ion can be repulsive when the two ions carrying like charges are brought closer and it counteracts to an energetically favored dispersion of the molecules. The strength of ion-ion interactions has a profound effect on several physical properties of pharmaceutical agents including salt selection, solid crystalline habit, solubility, dissolution, pH and pK determination and solution stability.

### Hydrogen bonding

One more type of attraction between molecules is hydrogen bonding. This bond arises when hydrogen atom is covalently bonded to a highly electronegative atom such as O, N, or F. Hydrogen attached to a triply bound carbon also forms hydrogen bonding. For example, HCN and  $\text{CHCl}_3$  form hydrogen bonds. The hydrogen bond formation in HF can be shown as below,



The dashed line indicates hydrogen bonding. The hydrogen bond is the electrostatic attraction between the F of one HF molecule and H of another HF molecule. The energy of hydrogen bond is about  $1/10^{\text{th}}$  of the energy of a covalent bond. The hydrogen bond may be *intermolecular* if it occurs between two same or different molecules (for e.g. hydrogen fluoride

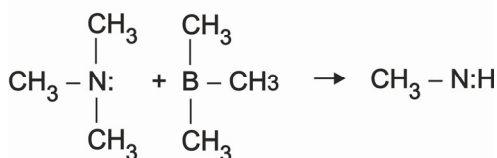
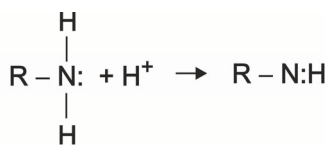
and water molecules) or *intra-molecular* if it occurs within a molecule. *Intra-molecular* hydrogen bonding occurs in 2-nitrophenol and salicylic acid. In the absence of hydrogen bonding, water would boil at a temperature well below 0°C. This hydrogen bonding increases the boiling point of water to 100°C. Carboxylic acid has higher boiling point due to hydrogen bonding. Hydrogen bonding is also responsible for high solubility of poly-hydroxy compounds such as sugar.

### Other types of bonds

Other types of bonds that may be worth mentioning are coordinate covalent bond and hydrophobic interaction.

#### Coordinate covalent bond

A coordinate covalent bond is formed when only one atom present in a molecule donates both the electrons for bond formation with another molecule. For example, the unshared electron pair in the nitrogen atom of an amine molecule (a Lewis base) can serve to form such a bond with a proton ( $H^+$ ) or with trimethyl boron (a Lewis acid).



Amine oxides are other examples of coordinate covalent compounds.



Coordinate covalent bond is also involved in the formation of complexes. In this, a pair of electrons in some degree is transferred from one interactant to the other interactant. The most important examples are the metal-ion coordination complexes formed in between metal ions (acting like acid) and bases. Such complexes can be viewed as products of *Lewis acid-base* reactions.

#### Hydrophobic interaction

The hydrophobic interaction of non-polar molecules or groups with each other in aqueous solution, arising because of the tendency of water molecules to exclude the non-polar molecules, is termed as hydrophobic interaction. In this, there is **no bond formation** but there is a tendency of water to exclude the non-polar molecules and in contact with water, the non-polar molecules



tend to associate together. This interaction is favored by an increase in entropy (degree of molecular randomness) of water molecules in the presence of non-polar molecules.

**b) Repulsive forces**

Intermolecular repulsive forces occur when two dipolar molecules are brought close together or when two molecules are brought so close so that their non-bonding electron clouds overlap or interpenetrate. This type of repulsive forces between the molecules decreases with distance of separation.

Another type of repulsive force is due to columbic repulsion existing between similarly charged ions. This repulsive force will be less if the ions are in a dielectric medium such as water.

Knowledge of these two types of opposing forces in molecules may help in understanding the physicochemical properties of gases, liquids and solids. To mention a few in pharmaceutical fields, it helps in understanding the solution process, interfacial phenomenon, complex formation process, and flocculation in suspensions, stabilization of emulsions, colloids, and compaction of powders in capsules. The possibility of compressing the granules into tablets and retaining the tablet shape may also be understood. An understanding of these intermolecular forces not only essential for predicting some physicochemical properties of various dosage forms but also helps in the interpretation of drug activation at the molecular level and for structure-activity correlations.

## 2. Temperature

The molecules, atoms or ions in the solid state are strongly held in close proximity by intermolecular, inter-atomic or inter-ionic forces respectively. We may call molecules, atoms and ions, in general, as particles. The particles held together in a solid substance can oscillate only about fixed positions. But, when the temperature of the solid substance is raised, the particles acquire sufficient thermal energy to disrupt the ordered arrangement of particles within the solid. This leads to weakening of the intermolecular forces causing at the same time increase in intermolecular distances also. As a result, the solid passes into liquid state.

The molecules in liquid state of the solid, on increasing the temperature further, pass into the gaseous state. In gaseous state, the intermolecular distances are greatly increased and the intermolecular forces are unable to act and come almost to nil. Therefore the molecules in the gaseous state exist individually with random motion.

In the transformation of solid to liquid and the liquid to gaseous state, heat is absorbed and the enthalpy (heat content) increases and the entropy (degree of molecular randomness) increases. That is, the ordered arrangement of particles in the solid is disrupted. When a change of state (also called phase change) occurs i.e. from solid to liquid or liquid to gas, the temperature remains constant. This means that when a sample of solid gets into liquid state at its melting

point, the temperature remains constantly at the melting point (temperature) until all the solid passes into liquid state. The heat supplied is absorbed by the molecules to go into the liquid state from solid state at the melting point and the heat absorbed is termed as *latent heat of fusion*. In general, during a change of state, the temperature remains constant but heat is absorbed until the conversion of state is completed and the heat absorbed is called as latent heat.

For example, when ice turns into water at its melting point of  $0^{\circ}\text{C}$ , heat is absorbed and that heat absorbed is termed as latent heat of fusion.

Therefore, the melting point of a solid is the temperature at which the solid is converted to a liquid state at atmospheric pressure and the heat absorbed during the phase change process is taken up as latent heat of fusion.

In the same way, when a liquid changes into gaseous state or vapor state at its boiling point, heat supplied is taken up as *latent heat of vaporization*. For example, if a sample of water is heated, the temperature raises steadily until it reaches its boiling point (i.e.  $100^{\circ}\text{C}$ ) at atmospheric pressure. This boiling point remains constant at  $100^{\circ}\text{C}$  until all the water is converted to vapor state. During this conversion process the heat absorbed is taken up as latent heat of vaporization.

The latent heat (of vaporization) absorbed, when water vaporizes is  $539\text{ cal/g}$  or about  $9720\text{ cal/mole}$ . This latent heat of vaporization is liberated when the vapors condense back into water.

The latent heat of fusion or the latent heat of vaporization will vary for different substances.

### **Sublimation**

Some solids may directly pass into gaseous state skipping the liquid state. In this case, change of state occurs directly from a solid state to gaseous state. This process is termed as *sublimation*. For example, camphor and iodine can undergo sublimation. That is solid camphor and iodine pass directly into vapor state.

The principle of sublimation is applied in the drying of substances that are highly heat sensitive. Drying refers to removal of water and this removal of water by means of sublimation is termed as *sublimation drying*. The other terms used are *freeze drying* or *lyophilization*.

Ice, water and water vapor can exist (solid, its liquid and its vapor) together at a temperature of  $0.0098^{\circ}\text{C}$  and a pressure of  $4.58\text{ mm Hg}$ . This temperature and pressure are called triple point temperature and pressure. Below this triple point temperature and pressure, sublimation can take place. That is, ice can be directly converted into (water) vapor by supplying heat under the triple point pressure. This conversion of ice directly into vapor is repeated several times until all the moisture (i.e. water) in the form of ice is driven away.

Moisture from drug substances or the solvent water in the solution of heat sensitive drugs (i.e. drugs that are decomposed by heat) can be removed by converting the moisture or solvent

water by freezing. From the frozen product, the ice (i.e. moisture or solvent water) can be removed by converting the ice directly into water vapor which is, then, removed. Moisture from biological drug products can be removed by lyophilization technique. By this way the stability of the drug product is enhanced. This technique is also used to prepare sterilized products.

### Gaseous state

Gases have the weakest forces of attraction of all the states. Almost all gases respond in a similar way to the variations of temperature, pressure, and volume.

Gases exert pressure on the containers in which they are contained due to vigorous and rapid motion with resultant collision among themselves and on the container wall. Given amount of gas occupies completely any available space. Suppose a gas is contained in a 100 cc bottle, it will occupy the whole 100 cc of the container. If the same amount of gas is contained in a 1000 cc of a bottle, it will occupy the whole 1000 cc of the container.

1. Gases are composed of particles which are atoms or molecules
2. Gas particles do not attract each other and hence can move freely within the container.
3. Gas particles move randomly owing to their kinetic energy.

Gas particles exhibit perfect elasticity. Hence, there will be no loss of energy or speed even if they collide among themselves or on walls of the container.

A gas is said to be ideal when the gas molecules exert no intermolecular forces or there is complete absence of attractive forces among molecules. Under such ideal situation, the general behavior of gases with variation of pressure, volume and temperature is given by ideal gas equations of *Boyle's* and *Gay-Lussac and Charles laws*.

*Boyle's law* states that pressure of a given mass of gas, at constant temperature, is inversely proportional to the volume.

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

Or  $PV = k$

The *Gay-Lussac and Charles law* states that the volume of a given mass of gas, at constant pressure, is directly proportional to absolute temperature.

$$V \propto T$$

Or,  $V = kT$

The above two equations can be combined to give the relationship

$$\frac{P_1 V_1}{T_1} = \frac{P_2 V_2}{T_2} \quad \dots 1.1$$

Where,  $P_1$ ,  $T_1$ , and  $T_1$  are the values of gas under one set of conditions and  $P_2$ ,  $V_2$ , and  $T_2$ , the values under another set of conditions. Therefore, it may be inferred that although  $P$ ,  $V$ , and  $T$  change, the ratio  $PV/T$  is always a constant and it may be expressed mathematically as

$$\frac{PV}{T} = R$$

or  $PV = RT$  ...1.2

This equation is applicable only for one mole of gas and for  $n$  moles of gas, the equation is

$$PV = nRT$$
 ...1.3

Where  $R$  = molar gas constant.

Rearranging the equation for volume,

$$V = \frac{nRT}{P}$$
 ...1.4

This equation is known as general ideal gas law or equation of state of an ideal gas. From the equation, it can be known that the volume of an ideal gas is directly proportional to number of moles and the absolute temperature and inversely proportional to pressure. The molar gas constant,  $R$ , can be given in different terms

When  $P$  and  $V$  are given in atmosphere and liters respectively, the value of  $R$  is  $0.0821 \text{ lit.atm.mole}^{-1}.\text{deg}^{-1}$

When  $P$  and  $V$  are given in dynes/cm<sup>2</sup> and cm<sup>3</sup> respectively, the value of  $R$  is  $8.314 \times 10^7 \text{ ergs mole}^{-1}\text{deg}^{-1}$  or  $8.314 \text{ joules mole}^{-1} \text{ deg}^{-1}$ .  $R$  is also  $1.987 \text{ cal mole}^{-1} \text{ deg}^{-1}$ , since  $4.184 \text{ joules}$  is  $1 \text{ calorie}$ .

When gases deviate from ideal behavior, they are termed as *real* or *actual gases* and may not obey the ideal gas equation strictly. The deviation from ideality becomes significant when the pressure becomes high and the temperature is very low because the molecules are in close proximity to attract each other. That is, the intermolecular forces operate. However, a majority of real gases and vapors at ordinary temperatures and pressures obey the law sufficiently accurate.

Where intermolecular attraction is significant between the real gas molecules under high pressure and low temperature, a modified equation is given by *van der Waals* and for 1 mole of real gas, the equation is,

$$P + \left(\frac{a}{V^2}\right) (V - b) = RT$$
 ...1.5

Where,  $a/V^2$  accounts for the internal pressure per mole. The *Van der Waals* 'a' is given in liter<sup>2</sup>atm per mole<sup>2</sup> for different gases. 'b' accounts for the compressibility of gas molecules or excluded volume and is given in liter/mole

For 'n' moles of gas, the equation is

$$P + \left(\frac{an^2}{V^2}\right)(V - nb) = nRT \quad \dots 1.6$$

### Pharmaceutical gases

Pharmaceutical gases include anaesthetic gases such as nitrous oxide and halothane. Compressed gases include nitrogen, carbon dioxide and oxygen for therapeutic uses. Liquefied gases are used as propellants in aerosol products. The gases used in aerosol products are certain halo-hydrocarbons and hydrocarbons.

Volatile liquids such as ether, halothane and methoxy fluorine are used as inhalation anaesthetics

Amyl nitrite is a volatile liquid inhaled for its vasodilatory effect in the treatment of angina.

### Liquid states

Liquids may be considered as solution of holes in material. That means there must be small spaces among liquid molecules. The space in liquids promotes the molecular motion. It explains the expansion of volume when materials (solids) undergo fusion. There is also decrease in viscosity and density as the temperature is raised.

In general, liquid is a substance that flows freely but is of constant volume. It is nearly incompressible and that confirms to the shape of its container but retains a constant volume independent of pressure.

The molecules of a gas are in a state of constant random motion owing to their kinetic energy. Kinetic energy is proportional to the absolute temperature of the gas. When a gas is cooled, the molecules lose their thermal energy and as a result their kinetic energy is greatly reduced. On further reduction of temperature, the molecules almost lose their kinetics energy and are not able to overcome the force of attraction. Closeness of the molecules promotes the molecules come closer and closer to exhibiting the intermolecular forces and the gas molecules ultimately get into liquid state.

The temperature at which a particular gas goes into liquid state is termed as *critical temperature*. Therefore, the critical point can be defined as the temperature above which a gas cannot be liquefied whatever be the pressure applied. That means pressure can be effective in liquefying a gas only below this critical (temperature) point. This critical temperature is, then,

defined as the temperature below which only, a gas can be liquefied by using pressure. Above this critical temperature, a liquid can no longer exist.

The critical temperature is different for different gases or vapors. (vapor of a liquid above its critical temperature is generally considered as a gas)

The critical pressure is the pressure required to liquefy a gas at its critical temperature. At critical temperature, the gas and its liquid become indistinguishable and the entropy (randomness) as well as the enthalpy (heat content) change is zero. For example, the critical temperature of water is 374°C or 647°K and its critical pressure is 218 atmospheres. Different liquids have different critical temperatures and pressures.

### ***Super critical fluids***

Now-a-days super critical fluids seem to assume some importance especially in food and natural products extractions and analysis.

When the temperature and pressure of a liquid crosses beyond the critical points, a super critical fluid may form. Under these highly stressed conditions, polar and non-polar fluids/liquids are completely miscible. For example, dense fluid solvents like super critical carbon dioxide and ethane have been shown to solubilize amino acids. They are also used in chromatography of polar drugs and elimination of toxic wastes.

### ***Liquefaction of gases***

When non-polar molecules are brought sufficiently close together, induced dipole-induced dipole or London attraction arises. These forces originate from molecular internal vibrations. The temporary dipoles that this vibration creates in the constituent atoms induce dipoles in the neighboring atoms of other molecules and this process induces a net attraction bringing the molecules still closer. This type of attraction (induced dipole-induced dipole attraction or London dispersion forces) is responsible for the liquefaction of non-polar gases. These inter-attractions involve energy of about 0.5 to 1 kcal/ mol.

Gases can be liquefied by the following methods. All these methods are based on the principle of bringing the gas molecules sufficiently close together to effect the liquefaction process.

1. By subjecting the gases to intense cold by the use of freezing mixtures.
2. By the use of adiabatic expansion (for ideal gases)
3. By the use of Joule-Thomson effect (for real gases)

Adiabatic expansion refers to a situation where an ideal gas is allowed to expand so rapidly that no heat enters the system (isothermally). The work done for the expansion is at the expense of its own internal heat energy content bringing down the temperature. The process is repeated

several times until the gas is liquefied. This can be carried out by using a *Dewar flask* or vacuum flask. It is related to the principles of thermodynamics.

Gases can be liquefied by using *Joule-Thomson effect*. In this method, a highly compressed real gas is allowed to expand into a region under low pressure where the energy is expended in overcoming the cohesive forces of attraction between the gas molecules. As a result, the temperature falls cooling the gas. Thus the gas is liquefied. However, this process needs pre-cooling of the gas. Liquid oxygen and liquid air can be obtained by this method.

### ***Vapor pressure***

When a liquid is in contact with its vapor, two opposing processes namely vaporization of the liquid into vapor and the condensation of vapor into liquid occurs. These two opposing processes continue till the pressure of the vapors ultimately reaches a value at which the rate of vaporization is equal to the rate of condensation i.e., equilibrium is reached. The pressure exerted by the vapor above the liquid at equilibrium conditions is termed as the *equilibrium vapor pressure* or simply the *vapor pressure*.

Liquids with low boiling point have high vapor pressure and liquids with high boiling point have low vapor pressure. The boiling point of a liquid, as we know, is the temperature at which the liquid boils under atmospheric pressure. In this case, the vapor pressure above the liquid (i.e. external pressure) equals the atmospheric pressure. By reducing the pressure above the liquid, we can make the liquid to boil under low temperature. We can also make a liquid to boil at a higher temperature by increasing the pressure above the liquid.

The relationship between the vapor pressure and the absolute temperature is given by *Claussius-Clapeyron* equation. The equation applies only to a narrow range of temperatures. The equation is,

$$\log \frac{P_2}{P_1} = \frac{\Delta H_v (T_2 - T_1)}{2303 RT_1 T_2} \quad \dots 1.7$$

Where,  $P_1$  and  $P_2$  are the vapor pressures at absolute temperatures  $T_1$  and  $T_2$  respectively.  $R$  is molar constant.

### ***Vapor pressure of miscible liquids***

In pharmacy, we use miscible liquids as well as immiscible liquids. Therefore, it is better to know the vapor pressure of such mixture of liquids. Miscible liquids can be considered as solution of the liquid in liquid. The partial vapor pressure exerted by each liquid is proportional to its molar concentration in the mixture solution. Suppose we have two liquids A and B. Then, the partial vapor pressure of liquid A is given by  $P_A^0 X_A$  and that of liquid B is  $P_B^0 X_B$ .

The total vapour pressure of two liquids is

$$P = P^{\circ}_A X_A + P^{\circ}_B X_B \quad \dots 1.8$$

Where,  $P^{\circ}_A$  and  $P^{\circ}_B$  are the vapor pressures exerted by the pure liquids A and B respectively.  $X_A$  and  $X_B$  are molar concentrations of liquids A and B respectively.  $P$  = total vapor pressure.

When a mixture contains two immiscible liquids, each liquid exerts its pressure independently of the other. The total vapor is, then given by,

$$P = P^{\circ}_A + P^{\circ}_B \quad \dots 1.9$$

Other properties of liquids considered in pharmacy are surface tension and viscosity.

### **Solid states**

Solids like liquids are practically incompressible. The intermolecular forces are strongest in solids. The molecules in solids can oscillate only about fixed positions. Solids may exist in *crystalline* or *amorphous* form.

#### ***Crystalline solids***

Solids that exist in different crystalline forms exhibit a high degree of order in crystalline states. They may be cubic (sodium chloride), tetragonal (urea), hexagonal (iodoform), rhombic (iodine), monoclinic (sucrose), triclinic (boric acid), etc.

The particles in solids are held together by different types of bonds. The bond types are metallic (metals), ionic (salts,) valence (diamond) and molecular (organic compounds). The distinguishing attributes are:

1. They have a fixed molecular order. It means the molecules occupy only set positions in a specific array.
2. They have a sharp melting points
3. They exhibit anisotropicity with the exception of cubic crystals. Anisotropicity refers to their properties which are not the same in all directions.

#### ***Amorphous solids***

The solids in which the atoms or molecules are arranged in a regularly repeating pattern are termed crystalline solids. In some other solids, there is no such characteristic regularity and hence they are termed as non-crystalline or amorphous solids or substances.

Amorphous solids or substances can be considered as super cooled liquids where the molecules are arranged in a random manner and they lack ordered arrangement. They do not have definite melting points. Glass, pitch and many synthetic plastics are amorphous solids.

Amorphous substances have high dissolution rate and hence their therapeutic action is enhanced through better absorption. For example, the crystalline form of the antibiotic



novobiocin acid is poorly absorbed and has no therapeutic activity, whereas its amorphous form is readily absorbed and hence has better therapeutic activity. The distinguishing attributes are

1. In these, the molecules are randomly arranged
2. They do not have a sharp melting point. The melting point is within a short range
3. They exhibit isotropicity. It refers to the properties which are same in all directions

### ***Polymorphism***

When a substance or compound such as cortisone acetate, exists in more than one crystalline form, it is said to exist in different polymorphic forms and this phenomenon is termed as *polymorphism*. When an element, such as sulfur, exists in different crystalline forms, then the phenomenon is termed as allotropy. However the terms polymorphism and allotropy are used interchangeably.

One polymorphic (or crystalline) form may change into another polymorphic (crystalline) form at a definite temperature. The temperature at which such polymorphic changes occur is termed as transition temperature. At transition temperature, both the forms will exist in equilibrium. The crystalline substance exhibiting this type of behavior is said to be enantiotropic. For example, rhombic sulfur is transformed into monoclinic form at the transition temperature of 368.50k. This transition can be reversed by cooling. That is monoclinic sulfur can be transformed into rhombic sulphur.

There are substances in which one polymorphic form can be transformed into another polymorphic form and not back into its original form. That is, they behave like one-way traffic. In these substances, transition can occur in one direction only and not in the reverse direction. Such substances exhibiting this type of polymorphism are called monotropic. For example, diamond can be transformed into graphite but not the graphite into diamond.

Polymorphism is an important factor to be considered in the pharmaceutical field. The polymorphic changes between different forms of fatty acids and glycerides are generally monotropic. For example, theobromo oil (otherwise called as cocoa butter) exists in four different polymorphic forms. They are metastable  $\gamma$ ,  $\alpha$ ,  $\beta'$  and stable  $\beta$  forms. Theobromo oil is used in the preparations of suppositories containing drugs. During the preparation, one must be careful to preserve the stable form which melts at 34.5°C to release the drug at body temperature. All the other forms  $\gamma$ ,  $\alpha$ ,  $\beta'$  melt at 18°, 22° and 28°C respectively. If the temperature is raised greatly above the melting point of the stable  $\beta$  form, the stable form will be destroyed and hence the suppositories cannot retain their shape at ordinary room temperature.

Polymorphism is possible in liquids also. For example, cholesterol acetate exists as clear and turbid solutions. These two polymorphic forms have different optical properties. The turbid form is termed as *liquid crystal*.

Different crystalline or polymorphic forms have different solubility and hence different therapeutic effects. Hence, it is pharmaceutically important to take into consideration the different polymorphic forms of drugs during the formulation of pharmaceutical dosage forms.

Thus, some drug substances exist in more than one crystalline and/or amorphous forms. In general amorphous forms are more soluble. Different polymorphic forms have different melting point, X-ray diffraction pattern, and different solubility. Many organic substances exhibit polymorphism. Some examples are aspirin, cortisone acetate, novobiocin sodium, methyl prednisolone, sulfathiazole, chloramphenicol, etc.

### ***Solvates***

Many pharmaceutical solids are often synthesized, purified and crystallized. When crystallized from solutions, the residual solvent can be entrapped in the crystalline lattice. This is something like a co-crystal of solid and solvent. The presence of the residual solvent may dramatically influence the crystalline structure of the solid depending upon the type of intermolecular interaction between the solid and solvent molecules. If water happens to be solvent, then, the solvate is termed as *hydrate*.

### ***Efflorescence, deliquescence and hygroscopicity in solids***

The pressure of water vapor in the atmosphere is  $13.33 \times 10^2 \text{ N/ m}^2$  at  $293^\circ\text{K}$ . A hydrated salt or a hydrate exerts greater vapor pressure than this and hence will tend to lose water. This phenomenon is called efflorescence. Hexa-hydrated sodium carbonate ( $\text{Na}_2\text{CO}_3 \cdot 6\text{H}_2\text{O}$ ) will tend to lose the water of crystallization to form a monohydrate ( $\text{Na}_2\text{CO}_3 \cdot \text{H}_2\text{O}$ ). as this monohydrate still exerts a greater vapor pressure, it tends to form anhydrous salt ( $\text{Na}_2\text{CO}_3$ ). However, this anhydrous salt exerts lower vapor pressure and gets hydrated immediately to monohydrate form. As a result, equilibrium is established instantly between the anhydrous and monohydrated forms of sodium carbonate.

The rate of efflorescence can be increased by heating. This process of acceleration of the rate of efflorescence in a hydrated salt is termed *exsiccation*. The anhydrous form of copper sulfate ( $\text{CuSO}_4$ ) can be obtained by exsiccation of penta-hydrated copper sulfate ( $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ ) at  $473^\circ\text{K}$  or  $200^\circ\text{C}$ .

There are some substances which take up water vapor from the atmosphere and become hydrated. Such substances are called *deliquescent substances* or *hygroscopic substances*. A deliquescent substance is one which will ultimately form a liquid phase by absorbing more moisture from the atmosphere whereas a hygroscopic substance is the one which takes up water but remains in the same solid state. In both the cases, the hydrated form must exert still a lower vapor pressure than that of the water vapor in the atmosphere. Otherwise (i.e. if it exerts greater vapor pressure), it will tend to lose water by efflorescence. Some deliquescent substances are potassium hydroxide, sodium lactate, potassium carbonate, etc. Examples for hygroscopic

substances are exsiccated sodium sulfate, ammonium chloride, etc. Glycerin, a liquid, is also hygroscopic substance. Semisolid wool fat is also hygroscopic.

Therefore, in the storage of deliquescent and hygroscopic substances a moisture-free atmosphere within the container must be ensured. Hence, they must be stored in well closed containers which prevent the access of water vapor into the containers. Additional protection for deliquescent and hygroscopic substances can be had by including a drying agent which takes up the water vapor in preference to the substances. Silica gel is often used for this purpose. If the silica gel has been saturated with moisture, it can act no more as a drying agent. Saturation of silica gel with moisture can be known by including cobaltous chloride which turns pink (from being blue) The pink color indicates that it can no longer act as a drying agent. In the case of efflorescent substances, the escape of moisture should be prevented with tightly closed containers.

### ***Humidity***

It is important to know about air-water vapor system, i.e., mixture of air and water vapor. The amount of water vapor present in the air refers to the concentration of water vapor in air and can be given in terms of percentage of water vapor in air. Actual amount of water vapor present in a given quantity of dry air can be given in terms of humidity. Humidity refers to the moisture content of air. There are different terms used to express the humidity. They are the absolute humidity, saturation humidity and relative humidity.

Absolute humidity is the amount of water vapor in Kg present in 1Kg of dry air.

The saturation humidity is the absolute humidity at which the partial pressure of water vapor equals the vapor pressure of pure water at a particular temperature.

The relative humidity is the one most often used and is the familiar expression of moisture content in the air. It is expressed as the ratio of actual concentration of water vapor in the air to the saturated concentration of water vapor in the air under the similar conditions of temperature and atmospheric pressure. Mathematically,

$$\text{Relative humidity (RH)} = \frac{\text{Measured vapor pressure of water vapor in air}}{\text{Saturation vapor pressure of water vapor in air}}$$

$$\text{Or} = \frac{\text{absolute humidity}}{\text{saturation humidity}} \times 100$$

Relative humidity is an important factor to be considered and controlled in the following operations.

1. In drying pharmaceutical products
2. In air conditioning
3. In the manufacture and filling of hard gelatin capsules (because hard gelatin capsules are hygroscopic in nature)
4. In the stability study of pharmaceuticals under controlled conditions
5. In the production of efflorescent products.

### **Intermediate states of matter**

Apart from the three major states of matter (solid, liquid, and gas), there exist some intermediate states also. They may be liquid crystals and glassy state.

#### ***Liquid crystals***

Liquid crystal can be considered as a state of matter between the liquid and solid. Some asymmetric molecules often exhibit such an intermediate fourth phase, liquid crystals or liquid crystalline state, apart from the three common states of matter, gas, liquid, and solid. They have the properties between those of conventional liquids (mobility and rotation) and those of solid crystals (birefringence). Birefringence is a property where when light passes through a solid crystal, it is divided into two components – the right circularly polarized light and left circularly polarized light with different velocities

They exhibit phase transition as a function of both temperature and concentration in a solvent especially water. That is, the liquid crystals can be formed either by heating of solids (thermotropic liquid crystals) or by the action of certain solvents on solids (lyotropic liquid crystals). The liquid crystals exhibit two main types of structures- the smectic, the molecules of which are mobile in two directions and show rotation about one axis and nematic, the molecules of which are mobile in three directions and can rotate about one axis. One more phase is called cholesteric phase which exhibits both nematic and smectic phases.

The liquid crystalline phases are believed to be involved in the stabilization of emulsions and solubilization of water insoluble materials. The liquid crystalline state is wide spread in nature and is found in cell membrane protein, and in nerves, brain tissue, and blood vessels.

#### ***Glassy state***

It is a state that combines some properties of solid crystals and some of liquids but is distinctly different from both. They have the mechanical rigidity of crystals and also the random disordered arrangement of molecules characteristic of liquids. That is, it differs from solids in not being structurally ordered but with some short range order. They do not have specific melting points as the solids do.

When a glassy former, in its liquid state, is cooled, it does not show drop in volume or density or in refractive index which the solids show at any particular temperature and when it passes through the freezing point (or melting point) to form a glassy state. It does not show a rapid drop in its volume as that of the super cooled liquid.

Atomically, the structure of the glassy state is found to be composed of a random selection of polyhedral molecules probably linked together at their corners. Formation of glass is easy with certain materials. Some glassy states are formed with difficulty. With some other materials, it is not possible. In general, glassy forming materials have a high viscosity at their melting point and this high viscosity prevents greatly the formation of ordered structure. Fig. 1. 2

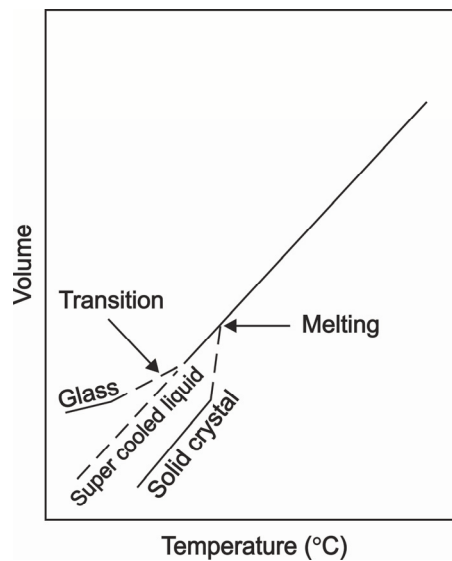


Fig. 1.2 Composite cooling curve of liquids forming super cooled liquid and solid crystals

Most of the glass formers are metal oxides. Formation of glasses depends on the nature of materials as well as the technique in crystallization process. The material, during crystallization, undergoes incomplete crystallization and that leads to the formation of glassy state.

### Mixtures of states of matter

Mixtures of states of matter may include physical mixtures of gas - gas, liquid - liquid, solid - solid, gas - liquid, gas - solid, and, solid - liquid. Such mixtures can also be solutions.

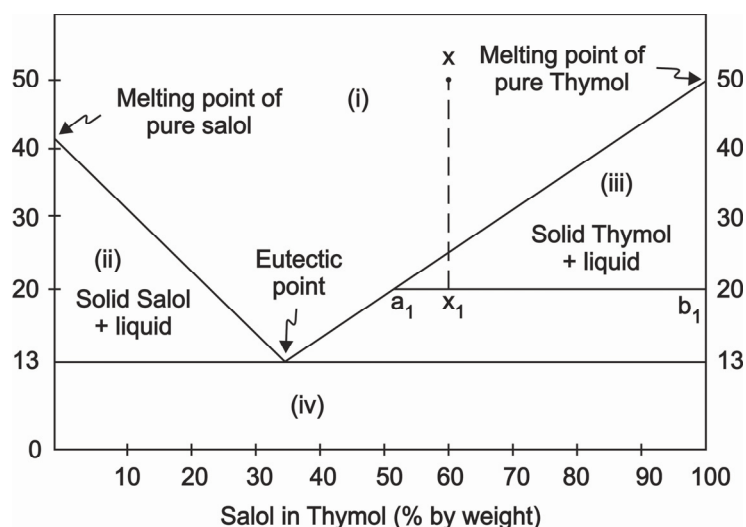
### Eutectic mixtures

We shall consider those of solid – liquid mixtures in which the two (solid) components are completely miscible in the melted liquid condition and completely immiscible as solids. That is, the solid phase that is formed from the liquid mixture (in the melted condition) consists of pure crystalline components.

Let us consider salol and thymol system as shown in Fig. 1.3. The phase diagram may be constructed first by determining the melting points of salol and thymol and cooling a series of binary solutions of compositions varying from pure salol to pure thymol. The phase diagram yields a V shaped curve and the points where the V shaped boundary of the melt intersects the left

and right vertical axes are the melting points of the pure salol and thymol respectively. The left arm of the V is the curve representing the temperature conditions under which various liquid mixtures are in equilibrium with the solid salol. The right arm of the V shows the various liquid mixtures that are in equilibrium with the solid thymol. The point where the two arms of the V shaped curve converges or meets is called eutectic point. In such a diagram, we find four regions:

1. A region (i) containing a homogeneous single liquid phase (in the melted condition). That is a binary solution of salol and thymol with different temperatures and compositions within the region
2. A two phase region (ii) containing a conjugate liquid phase of salol in thymol and solid salol.
3. A two phase region (iii) containing a conjugate liquid phase of thymol in salol and solid thymol.
4. A two phase region (iv) containing solid salol and solid thymol as eutectic mixture.



**Fig. 1.3 Temperature phase diagram of Thymol-Salol system showing eutectic point**

The regions (ii, iii) containing two phases are comparable to the two-phase region of the phenol - water system. Therefore, it is possible to calculate both the composition and relative amount of each phase (in the example considered- a conjugate melt i.e. liquid phase and a solid phase) at any point on the tie line drawn parallel to abscissa, at a particular temperature, joining the boundaries in the respective region. The vertical axis denotes the solid phase of either salol or thymol depending on the region considered and the left and right arms of the curve V, give the varying compositions of the liquid phase.

At the point, where the two arms of the V converge or meet, both solid salol and solid thymol are in equilibrium with the liquid solution forming three phase system and at this point, called the eutectic point, any of the possible combinations of liquid solutions of salol and thymol will freeze. This eutectic point, which occurs at the lowest temperature, is the point at which the liquid phase can exist. In other words, it is the lowest melting point of any possible mixture of solid salol and thymol. Only at this point, the composition of the solid mixture is same as that of the liquid mixture from which it separates or crystallizes. Thus, at the eutectic point, both salol and thymol come out together in a constant proportion. Therefore, *eutectic point* may be defined as the lowest melting of the binary solution and at this point, three phases solid salol, solid thymol and a liquid phase coexist. At this point, the degree of freedom is zero. Alternatively, a *eutectic composition* is the composition of two or more compounds that exhibits a melting temperature lower than that of any other mixture of the compounds.

This eutectic composition is a simple two-phase mixture. As it is made *in situ*, it has a very fine-grained structure that could impart to it different properties (e.g. solubility) from that of a gross mixture of the same composition. For salol-thymol system, the eutectic point occurs at the composition of 34% of thymol in salol and for it, the lowest melting point, i.e. eutectic temperature, is 13°C.

Solid ice and potassium chloride will also form eutectic mixture. In this case, the mixture of ice and potassium chloride will give a freezing mixture to generate temperatures as low as -15°C, very below the freezing point of water. The effect of freezing mixture can be explained as follows: If a salt as such potassium chloride is added to ice and a little water the salt will dissolve to give a system composed of the three phases, solid ice, solution of the salt, and the solid salt. Such a system will be stable only at eutectic temperature or eutectic point. The system, therefore, tends to move towards this point and ice will melt and the salt will continue to dissolve. Both of these processes are accompanied by the absorption of heat and the temperature, therefore, falls until one of the solid components has been used up completely. By choosing suitable proportions of solid ice and salt, eutectic temperature can be reached.

Mixtures of any two of the substances such as *camphor, salol, chloral hydrate, thymol, menthol, and beta-naphthol* form similar eutectic mixtures.

Substances forming eutectic mixture produce a solution on mixing. Such substances, in dry form, can be dispensed by the addition of an absorbent powder such as kaolin or light magnesium oxide or carbonate.

### ***Liquid complexes***

These are mixtures that have a co-existence of two phases solid/liquid (suspensions, gas/solid (granular substances), liquid/gas (foams), and liquid/liquid (emulsions). The liquid complexes exhibit unusual mechanical properties to the application of stress or strain due to

geometrical constraints that the phases co-exist impose. The mechanical response includes transition between solid-like and fluid-like disorder as well as fluctuation. The mechanical properties can be attributed to the characteristics such as high disorder, aging, and clustering of multiple length scales.

### ***Aerosols (solid or liquid solution in gas)***

Liquids obtained by liquefying gases under pressure (or by cooling) revert to the gaseous state when the pressure is reduced. That is, liquid molecules expand to revert to its original gaseous state. Aerosols are based on this simple principle of reversible change of state on the release of pressure. This reversible change of state is the basic principle involved in the preparation of pharmaceutical aerosols. The term *aerosol* is used to denote various systems ranging from those of colloidal nature to systems consisting of pressurized packages

In pharmaceutical aerosols, liquefied gas (also called liquefied gas propellant or liquid propellant) is sealed within an aerosol container with the drug product concentrate dissolved or suspended. Within the container equilibrium is quickly established between the gaseous propellant which occupies the space above the liquid propellant in the container and the liquid propellant with any drug product concentrate under normal atmospheric conditions. If the pressure within the container is reduced by pressing the aerosol valve, it will force the liquid up the tube in the aerosol container and out of the orifice of the valve into the atmosphere. In aerosol container, only a momentary reduction in pressure occurs upon pressing the valve and releasing.

When the drug product concentrate together with the liquid propellant comes out, the drug product concentrate is sprayed as air borne liquid droplets in the case of drug in solution or as fine drug particles in the case of drug concentrate in suspension. As the liquid phase is expelled from the container, equilibrium is established instantly. Thus the pressure remains virtually constant in the container until the liquid propellant containing the drug is depleted.

Filling of aerosol containers can be achieved either by cooling the propellant and drug to a low temperature within the container itself and then the container is sealed with a valve.

Another method involves sealing the drug concentrate within the container and then forcing the required amount of propellant into the container under pressure. This is termed as pressure filling.

Aerosols have clear advantage over conventional dosage forms. The antiseptic formulation can be sprayed on the affected part with minimum discomfort for the patient. Ethyl chloride can be sprayed on the skin to freeze (i.e. to make the skin tissue insensitive) for performing minor operations. This offers easy handling also.

Chlorofluorocarbons and hydrofluorocarbons have been in use traditionally as propellants in aerosol products. Environmental concerns (ozone depletion) have led to the increased use of other



gases such as nitrogen, carbon dioxide and nitrous oxide. Moreover these gases are acceptable for use in pharmaceutical field. By varying the proportions of various propellants, pressures within the container ranging from 1 to 6 atm at room temperature can be attained.

Topical pharmaceutical aerosols can be formulated as a spray, foam, and semisolid and can be used to deliver the drugs topically to the skin surface, rectally, and vaginally. They consist of a liquid, emulsion, or a semisolid concentrate and a liquefied or compressed gas propellant.

### ***Inhalers (inhalation aerosols)***

The ease of application of medications into the body cavities using the principle of aerosols has led to the development of inhalation aerosols or simply inhalers. Inhalers are mainly administered for their local action on the bronchial tree. They are also used for producing systemic effects through absorption from lungs.

Drugs, which are delivered via a nebulizer or atomizer, are formulated as aqueous solutions or suspensions. The patient can inhale the drug through the atomizer or nebulizer, or other devices. There are dry powder inhalers also where a single dose of drug powder packaged in capsule is punctured and released into a chamber of the device and the patient can inhale the drug powder. These dry powder inhalers have now been replaced by metered dose inhalers (MDI).

The metered dose inhaler consists of a pressurized container filled with therapeutic agent (i.e drug), excipients and propellant and a metered dose valve. During use, an exact amount of therapeutic agent is expelled in the proper particle size distribution to achieve maximum introduction of drug into the lungs. Metered dose inhalers are formulated as solutions or suspensions of therapeutic agent in a mixture of solvents, dispersing agents, and liquefied gas propellants.

### **Physicochemical properties of molecules**

The properties exhibited by a molecule depend on intermolecular attractions and repulsions mentioned earlier. The energy within a molecule is determined by its unique composition of the molecule. In macromolecules like proteins or synthetic polymers presence of dipole interaction, steric hindrance, repulsive forces, *Van der Waals* forces all contribute to distortions in the primary intermolecular bonding energies. In addition, there may be rotational and vibrational energies. In general, physical properties of substances may be classified into colligative, additive, and constitutive.

The bonding order of atoms in a molecule may confer on the molecule what are called as *constitutive* and *additive properties*. Constitutive property depends on the arrangement of atoms within a molecule. This provides knowledge on the constitutive of individual molecule and groups of molecules. Optical rotation is a constitutive property. Molecular weight, which is the sum of masses of each atom in the molecule, is the additive property. If a solution contains two or

more substances, mass of each component contributes to the total mass of the components and it is an additive property. Many properties of substances may be partly constitutive and partly additive. For example, the refraction of light, electric properties, surface and interfacial characteristics etc exhibit both constitutive and additive properties.

The constitutive and additive properties influence many physical properties of molecules. With a knowledge of specific physical properties and the chemical nature of closely related molecules, it may be possible to describe the spatial arrangement of atoms in the molecules of a drug compound and provide evidence for the relative physical and chemical behavior of the molecule. Knowledge of spatial arrangement of atoms in the molecule and the relative physical and chemical behavior may serve as tool for the creation of new molecules with selective pharmacologic activity. Specific physical property and chemical nature of drug molecules may also suggest methods for qualitative and quantitative analysis of a pharmaceutical agent. The qualitative and quantitative analysis may help the researcher for drug design and wide range of methods for assessing the quality of drug products.

Recently the development of computational tools, depending solely on physical properties of molecules, are sought to develop molecules with ideal physical properties. The computational modeling is extensively used in drug discovery and drug design for better and desired pharmacological actions.

For our study, only a few physical properties will be considered required for physical pharmaceutics subject.

### ***Refractive index***

The speed with which the light travels through vacuum is reduced when it passes through a substance. That is, light passes more slowly through substances as a result of interaction with the molecules of substances.

When the light passes from the lighter medium through denser medium, the light wave is bent toward the interface separating the two media. This phenomenon of bending the light is called refraction. The velocities of the light through the lighter medium and denser medium are related to the sine of angle of the incident ray of light and the sine of angle of the refracted ray of light

The relative value of the effect of refractions between the lighter and denser medium is given by refractive index.

$$n = \frac{\sin i}{\sin r} = \frac{\text{velocity of light in the lighter medium } (c_1)}{\text{velocity of light in the denser medium } (c_2)} \quad \dots 1.10$$

$\sin i$  = sine of angle of incident ray of light

$\sin r$  = sine of angle of refracted ray of light

$c_1, c_2$  are the velocities of light in the respective medium.

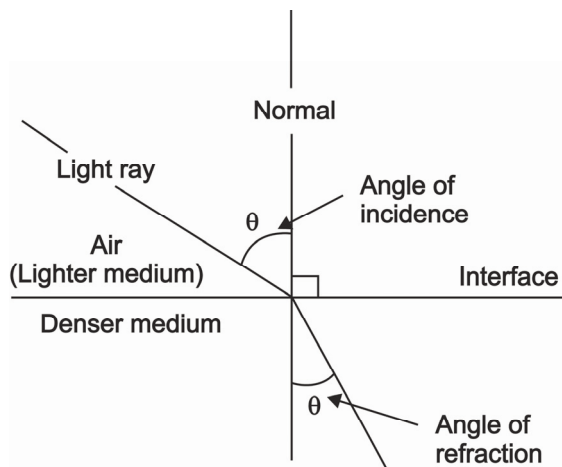


Fig. 1.4 Light passing an interface between air and denser medium

Conventionally, the refractive index is expressed with respect to the velocity or speed of light in air and compared to the velocity or speed of light in the substance to be studied because the deviation is only 0.03 % from that in a vacuum.

The refractive index varies with the wavelength of light and temperature because both of them influence the energy of interaction between the light and the medium. Hence, for practical purposes, the refractive index is calculated by using a light of finite wavelength at definitive temperature.

The instrument used for the measurement of refractive index is called *Refractometer*. It is used for studying pharmaceutical compounds that will not undergo extensive uv-visible absorption.

Refractive index can be used to identify a substance, to know the purity of the substance and to determine the concentration of a substance in an aqueous solution.

### **Optical rotation**

Electromagnetic radiation is a form of energy. It comprises both oscillating electric and magnetic fields at right angles to each other. The knowledge about atomic and molecular structure comes from the interaction of these two components – electric and magnetic field components. A source of light will produce multiple waves of oscillating electromagnetic radiations at a given time. In the study of optical rotation, we are concerned with electric component of radiation. Fig. 1.5

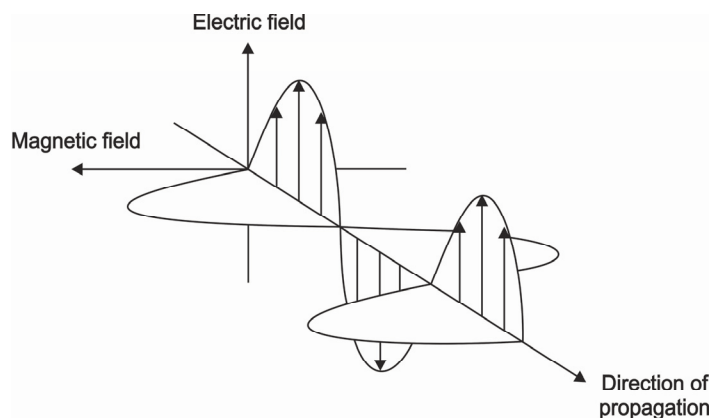


Fig. 1.5 Oscillating electric and magnetic field

When light passes through a polarized prism such as *Nicol prism*, only those vibrations occurring in a single plane are allowed to pass from that of randomly distributed vibrations of electric radiation. Such a light is plane polarized light. Fig. 1.6

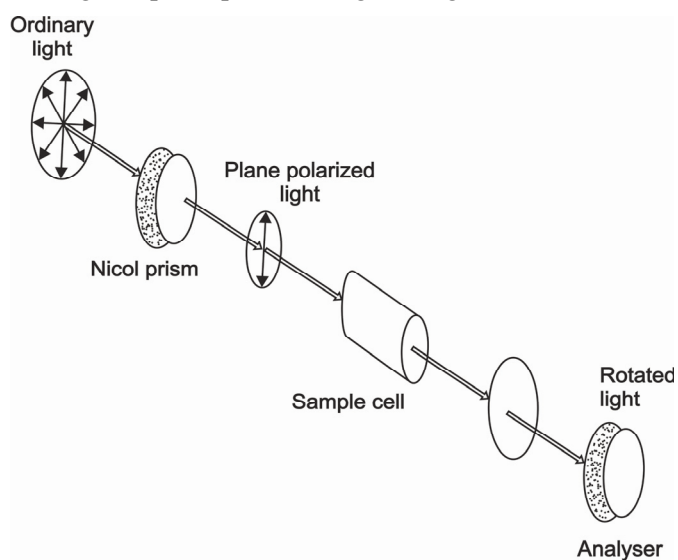


Fig. 1.6 Polarimeter (schematic)

The velocity of the plane polarized light can be slower or faster, when it passes through a sample of solution of an optically active substance, as mentioned in refraction. This change in velocity results in refraction of the plane polarized light for an optically active substance. A clockwise rotation of plane polarized light indicates the substance studied is dextrorotatory. When the plane polarized light is rotated by the sample of solution in a counter clockwise direction, the sample is to be identified as levorotatory substance. The angle of optical rotation,  $\alpha$ , produced by dextrorotatory substance is taken as positive. The angle of rotation,  $\alpha$ , produced by levorotatory substance is taken as negative. Only the molecules that have an asymmetric center (*chiral*

compounds) are optically active. Symmetric molecules (*achiral* compounds) are optically inactive.

In the case of refraction, the denser the medium through which the light passes, the greater will be the angle of deviation. In a similar way, the optical rotation depends on the density of an optically active substance.

A specific rotation,  $\alpha$ , at a specified temperature and wavelength,  $\lambda$  (usually the D-line of sodium), is characteristic for a pure, optically active compound. Specific rotation is indicative of molecular structure. Specific rotation may be used to identify a synthesized compound. This method offers to check the identity and purity of a reaction product. When specific rotations are reported, the solvent used, concentration studied should be reported along with the temperature used.

Drugs such as ampicillin, benzyl penicillin are dextrorotatory. Drugs such as nicotine and reserpine are levorotatory.

### ***Dipole moment***

In polar molecules such as hydrogen fluoride, the separation of charges can be permanent ( $\text{H}^+ : \text{F}^-$ ) and the molecule will possess a permanent dipole moment,  $\mu$ . However, those charges balance each other and as a result, the molecule *does not have a net charge* irrespective of charge separation. When no charges exist in molecules, a measure of their polarity (i.e., the electronic or charge distribution within the molecule) is given by the property called the *dipole moment* ( $\mu$ ). The process by which dipole arises due to differences in electronegativities of the atoms in a molecule is known as polarization. *Polarizability* indicates the ease with which an ion or molecule can be polarized by any external source such as electric field, light energy, or through interaction with another molecule. (Large anions have large polarization because of their loosely held outer electrons).

The magnitude of permanent dipole moment is, however independent of any induced dipole in the electric field. Therefore, the dipole is defined as the sum of individual charge moments within the molecule itself. This includes those from bonds and lone pair electrons. The dipole moment depends on the distance of separation between charges. The unit of dipole moment,  $\mu$  is debye ( $1 \text{ debye} = 10^{-18}$  electrostatic units cm)

Molecules with permanent dipole can also have induced dipole, when put in an electric field. Maximum dipole moment may be expected if the molecules are perfectly oriented with respect to electric field. However, absolute perfect orientation is prevented by the thermal motion of the molecules. The total polarization (P) of the molecule in an electric field is given by

$$P = P_i + P_o = \left( \frac{\epsilon - 1}{\epsilon + 2} \right) \frac{M}{\rho} \quad \dots 1.11$$

Where  $\epsilon$  = dielectric constant,  $M$  = molecular weight  $\rho$  = density and  $P_o$  = orientation polarization of the permanent dipoles in electric field and is equal to  $4\pi N\mu^2/9kT$  where  $k$  = Boltzman constant  $1.38 \times 10^{-23}$  joule/K and  $N$  = Avogadro's number ( $6.03 \times 10^{23}$  per mole).

The above equation  $P = P_i + P_o$  can be written in a linear form as

$$P = P_i + A \left( \frac{1}{T} \right) \quad \dots 1.12$$

The  $P$  (total polarization) values, found at different temperatures, are plotted against  $1/T$  values. The slope  $A$  is given by  $4\pi N\mu^2/9k$  and  $P_i$  is obtained from the intercept. From the  $P_i$ , polarizability ( $\alpha_p$ ) of the molecule can be calculated using the equation  $4/3\pi N \alpha_p = P_i$ . From the slope of the graph, the dipole moment ( $\mu$ ) can be calculated.

The value of  $P$  can be obtained by measuring the dielectric constant and density of the polar compound studied at various temperatures and using the equation

$$P = \left( \frac{\epsilon - 1}{\epsilon + 2} \right) \frac{M}{\rho} \quad \dots 1.13$$

Though covalent bonds are formed in the carbon dioxide molecule ( $O=C=O$ ), the dipole moment is zero because of its symmetric structure. Benzene and p-chloro benzene are symmetric planar molecules and hence those molecules have no dipole moment.

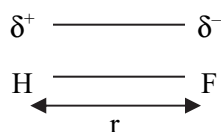
Water has a high dipole moment and can interact with solutes to cause solution. This interaction contributes to the solvent effect. In the case of water, the interaction is associated with the hydration of ions and molecules.

Induced dipole interactions do play a role in solubility phenomena. Dipole interactions which promote drug-receptor binding are essential in eliciting pharmacological actions of drug molecules.

Correlation of biological activity with dipole moment has been reported for the insecticidal activity of chlorophenothane (DDT, dichloro di-phenyl tri-chloroethane) isomers, the cholinesterase inhibiting activity of *N-alkyl* substituted amines and the respiratory stimulation activity of cyclic ureas and cyclic thiourea.

### **Dielectric constant**

A dipole is a separation of two opposing charges over a distance  $r$ .



Dipole is described by a vector whose magnitude is given by  $\mu = q r$

For two charges separated by a distance  $r$ , the potential energy is given by Coulomb's law

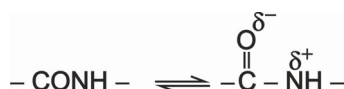
$$U_{(r)} = \frac{q_1 q_2}{4 \pi \epsilon_0 r} \quad \dots 1.14$$

When  $q_1$  and  $q_2$  are charges in Coulomb's,  $r$  is distance of separation in meter and  $\epsilon_0$  is permittivity constant of the medium in which the molecule is placed.

Different solvents have different permittivity. Permittivity is a material property that affects the Coulomb's force between the point charges. Relative permittivity of a material is its permittivity expressed as a rate permittivity relative to the vacuum permittivity.

Symmetric molecules have no dipole moment. The reason is, there is no charge separation as in  $H_2$ , or there is cancellation of the dipole vectors as in  $CO_2$  ( $O=C=O$ ).

Separation of electric charge can be maintained through induction by an electric field or by a permanent charge separation in a polar molecule. The dipolar nature of peptide bond is an example of permanent dipole.



It is better to understand the concepts of polarity and dielectric constant.

Consider two parallel electricity conducting condenser plates separated by a medium across a distance, 'd' and connected to a battery as shown in Fig. 1.7

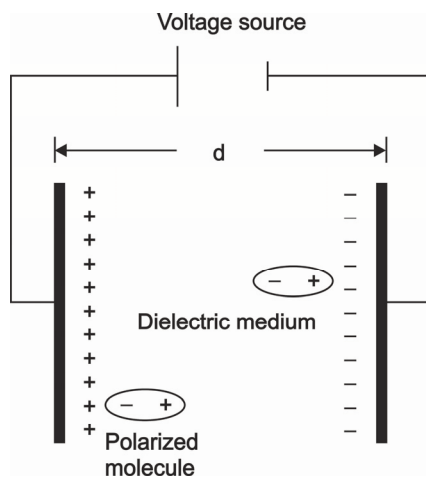


Fig. 1.7 Parallel plate condenser

Electricity from battery will flow from the left plate to the right plate until the potential difference between the two plates is equal to that of the battery supplying the initial potential

difference. The capacitance of the condenser plate is then equal to the quantity of charge  $q$  (in Coulombs) stored on the plates divided by the potential difference in volts,  $V$ , between the plates separated by a distance,  $d$ .

$$C = \frac{q}{V} \quad \dots 1.15$$

When a vacuum fills the space (i.e. as medium) between the two plates, the capacitance,  $C_o$  is

$$C_o = \frac{q_o}{V_o} \quad \dots 1.16$$

When water or any material fills the space between the two plates, the capacitance  $C_x$ , is

$$C_x = \frac{q_x}{V_x} \quad \dots 1.17$$

The value  $C_o$  is taken as a reference to compare capacitances when other substances fill the space between the plates. Then, the capacitance of the condenser plates filled with some material,  $C_x$ , divided by the reference standard,  $C_o$  is referred to as the dielectric constant,  $\epsilon$ ,

$$\epsilon = \frac{C_x}{C_o} \quad \dots 1.18$$

Thus, the ratio between the capacitances gives the dielectric constant of the material with respect to vacuum.

The dielectric constant is a measure of the ability of a molecule to resist charge separation. If the ratios of capacitances ( $C_x / C_o$ ) are close, the resistance to charge separation in the molecule will be greater. As the ratios increase, the ability to separate charges is increased.

Dielectric constants give the ability of solvent in dissolving drug substances.

### **Dissociation constant**

One of the physical properties of substances is colligative property. Colligative properties depend solely on the number of particles existing in a solution and they are influenced by association and dissociation of molecules. The colligative properties are *lowering of vapor pressure, elevation of boiling point, depression of freezing point and osmotic pressure*.

The solutes (whether gases, liquids, or solids) can, in general, be classified into *non-electrolytes* and *electrolytes*

Non-electrolytes are substances which do not undergo ionization or dissociation (separation into positive and negative ions) when dissolved in water to form a solution and therefore they do not conduct electric current through the solution. Some examples are sucrose, glycerin, urea etc.,. Equal concentrations of different non-electrolyte solutions exhibit approximately the same colligative effects.



Electrolytes, on the other hand, dissociate into ions in aqueous solutions. They conduct electric current. The solutions of electrolytes show anomalous colligative property irrespective of the same concentration because the number of particles may differ due to association or dissociation. Examples of electrolytes are hydrochloric acid, sodium chloride, ephedrine and Phenobarbital.

Electrolytes may, again, be subdivided into *strong and weak electrolytes*. This subdivision depends upon whether the electrolyte completely ionizes or partly ionizes in aqueous solutions. For example, hydrochloric acid is a strong electrolyte which ionizes into  $\text{H}^+$  and  $\text{Cl}^-$  ions in water completely whereas acetic acid is a weak electrolyte which ionizes only partly as  $\text{CH}_3\text{COO}^-$  and  $\text{H}^+$ . Weak base such as ammonium chloride also ionizes partly into  $\text{NH}_4^+$  and  $\text{OH}^-$ . Strong electrolytes include solutions of strong acids, strong bases, and most salts. Weak electrolytes include weak acids and bases, primarily organic acids amines, and a few salts.

Most of the drugs are weak electrolytes. That is, they may be weak acids (e.g. phenobarbital) or weak bases (e.g. ephedrine). Weak acids and weak bases ionize or dissociate only partly and the extent or degree of dissociation can be known from the dissociation constant. As we are concerned with dissociation (i.e. ionization) constant, we will consider substances which are weak acids and bases. Dissociation of electrolytes occur mainly in their aqueous solutions.

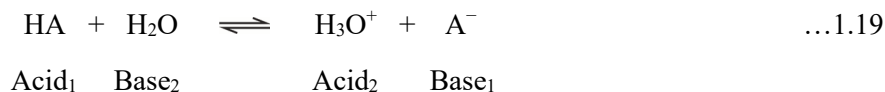
Solvents can be classified as *protophilic, protogenic, amphiprotic, and aprotic*. A protophilic solvent can accept protons from the solute. For example, acetone, ether, and liquid ammonia are protophilic solvents. Compounds such as formic acid, acetic acid, sulphuric acid, liquid hydrochloric acid, and liquid HF are proton-donating (i.e. protogenic) solvents. Amphiprotic solvents act as both proton acceptors and proton donors. Water and alcohols are amphiprotic solvents. Aprotic solvent, as the name indicates, neither accept nor donate protons. Examples of aprotic solvents are hydrocarbons.

### **Importance of dissociation constant**

What is the need to know about the dissociation constant? As most of the drugs are weak acids or bases, they exist in aqueous solutions as partly undissociated and as partly dissociated forms. Though the dissociated and the undissociated forms of a drug are in solution, the undissociated forms are better absorbed than the dissociated forms. But, this dissociation and undissociation of the drug depend on the pH of the solution. In the event of any unfavorable pH change, the undissociated forms of the drug may get precipitated leading to instability or in the event of dissociation due to pH change, the dissociated forms of the drug are not better absorbed. Hence, a compromise is necessary between the pH and solubility. In this context, the dissociation constants of drugs assume importance for our consideration.

**Acidity and basicity constants**

Before we proceed to the study of dissociation constant, it is worthwhile to refresh the knowledge about the ionization of weak electrolytes such as acetic acid. In general, the ionization of a weak acid which ionizes incompletely in water may be given as



Introducing the concentration terms for the above reaction, we can write,



According to Law of mass action, the rate of forward reaction ( $R_f$ ) is proportional to the concentration of the reactants and the rate of backward or reverse reaction ( $R_r$ ) is proportional to the concentration of the products.

Introducing a constant  $K$ , the forward reaction  $R_f$  is,

$$R_f = K_1 [\text{HA}] [\text{H}_2\text{O}] \text{ and the reverse reaction } R_r \text{ is}$$

$$R_r = K_2 [\text{A}^-] [\text{H}_3\text{O}^+]$$

At equilibrium,  $R_f = R_r$

$$\text{Therefore, } K_1 [\text{HA}] [\text{H}_2\text{O}] = K_2 [\text{A}^-] [\text{H}_3\text{O}^+]$$

(The student must understand that the concentrations of the reactants and products may or may not be equal. It is the speed or the rate of the forward and reverse reactions that are equal)

Solving for  $K_1/K_2$ , we can obtain,

$$\frac{K_1}{K_2} = \frac{[\text{A}^-][\text{H}_3\text{O}^+]}{[\text{HA}][\text{H}_2\text{O}]}$$

Replacing  $K_1/K_2$  by  $K$ ,

$$K [\text{H}_2\text{O}] = \frac{[\text{A}^-][\text{H}_3\text{O}^+]}{[\text{HA}]} \quad \dots 1.21$$

As water is in great excess in dilute acetic acid solution, it may be considered as constant at about 55.3 moles/liter. (1 liter water at 25°C weighs 997.07g and  $997.07/18.03 = 55.3$  moles/liter, where 18.03 is the molecular weight of water). This value (55.3) may be combined with  $K_1/K_2$  to obtain a new constant  $K_a$ , (i.e.  $K \times [\text{H}_2\text{O}]$ )

$$K_a = \frac{[\text{A}^-][\text{H}_3\text{O}^+]}{[\text{HA}]} \quad \dots 1.22$$

Where,  $K_a$  is ionization constant. Here, we are concerned with acid and hence a better term for ionization constant of weak acid is *acidity constant*.

The dissociation constant of weak acid at 25°C such as acetic acid is given as  $1.75 \times 10^{-5}$  i.e. 0.000075 moles/liter. From this value, one can understand, in general, the slight degree of dissociation of weak electrolytes.

In the same way, the *basicity constant*,  $K_b$ , can be derived for a weak base such as ammonia ( $\text{NH}_3$ )



In general, the reaction for weak base is,



The equilibrium expression for this reaction is

$$K = \frac{[\text{BH}^+][\text{OH}^-]}{[\text{B}][\text{H}_2\text{O}]} \quad \dots 1.25$$

$$K_b = \frac{[\text{BH}^+][\text{OH}^-]}{\text{B}} \quad \dots 1.26$$

Where,  $K_b$  is basicity constant which is  $K \times [\text{H}_2\text{O}]$

*Dissociation constant* is a general term applicable for both acidity constant and basicity constant.

### Determination of dissociation constant

The dissociation constant for a weak acid or base can be obtained by various methods such as conductivity measurements, visible or ultraviolet absorption spectroscopy, potentiometry etc.

Of these methods, the potentiometric pH measurement is the most widely used. The principle involved in this method is very simple. It may be determined from the equation (1.22) which is again given below,

$$K_a = \frac{[\text{A}^-][\text{H}_3\text{O}^+]}{[\text{HA}]} \quad \dots 1.27$$

When the equimolar concentration of the salt,  $[\text{A}^-]$  (which is obtained from the ionization of the salt) and  $[\text{HA}]$ , the acid, are present, the dissociation constant,  $k_a$ , is numerically equal to the hydronium ion concentration.

i.e.  $K_a = [\text{H}_3\text{O}^+]$ , when  $[\text{A}^-] = [\text{HA}]$

What one has to do is to measure the pH of a solution containing equimolar concentrations of the acid and a strong base salt of the acid. (for example, by measuring the pH of the mixture

containing equal concentration of potassium acetate and acetic acid). At this concentration pH is equal to  $pK_a$ . From  $pK_a$ , the dissociation constant,  $K_a$  can be calculated.

Though this method is simple and rapid, it is not sufficiently accurate. For a high degree of accuracy and precision, a dilute solution of the weak electrolyte such as acetic acid is titrated against a strong base (such as potassium hydroxide). After each increment of addition, the pH of the resulting solution is determined potentiometrically.

The proton balance equation for the above mentioned titration of the weak acid against the strong base would be,

$$[K^+] + [H_3O^+] = [OH^-] + [A^-] \quad \dots 1.28$$

Where  $[K^+]$  represents the concentration of the base (KOH) added.

By rearranging the equation,

$$[A^-] = [K^+] + [H_3O^+] - [OH^-] \quad \dots 1.29$$

Replacing  $[A^-]$  by Z, we obtain,

$$Z = [K^+] + [H_3O^+] - [OH^-] \quad \dots 1.30$$

For monoprotic acid (i.e. acids containing one hydrogen), the sum of both unionized and ionized species, after equilibrium has been established, must be equal to  $c_a$ , the stoichiometric (added) concentration of the acid or,

$$C_a = HA + [A^-] \quad \dots 1.31$$

Replacing Z for  $[A^-]$ , we get

$$C_a = HA + Z \quad \dots 1.32$$

Rewriting the equation (1.27) here,

$$K_a = \frac{[H_3O^+][A^-]}{[HA]} \quad \dots 1.33$$

And on rearranging, we obtain

$$HA = \frac{[H_3O^+][A^-]}{K_a} \quad \dots 1.34$$

Substituting for  $[HA]$  in the equation (no 1.32), we get,

$$C_a = \frac{[H_3O^+]Z}{K_a} + Z \quad \dots 1.35$$

This, on rearrangement, yields

$$Z = C_a - \frac{Z [H_3O^+]}{K_a} \quad \dots 1.36$$

If  $Z$  values are plotted against the values of  $Z [H_3O^+]$ , a straight line is obtained with a slope. The slope is equal to  $1 / K_a$  and the intercept obtained by extrapolation gives the value of  $c_a$ . From the value of  $1 / K_a$ , the value of dissociation constant,  $K_a$  can be obtained. This method can be used to the substance titrated which cannot be purified or for a substance whose degree of solvation is unknown.

### Degree of dissociation

Drugs may be pharmacologically active in undissociated or in dissociated form. Drugs such as anionic and cationic antibacterial and anti-protozoal agents are more active when in the ionic state. Other compounds, such as hydroxybenzoate esters and many general anaesthetics are active in undissociated form. There are compounds such as sulphonamides which are considered to be effective both as ions and as neutral molecules.

Degree of dissociation is also a criterion to classify solutes into strong and weak electrolytes. Hence, degree of dissociation assumes some importance.

*The degree of dissociation (or ionization) for weak electrolytes (weak acid or base) can be obtained from the ratio of conductance of an electrolyte at any specific or given concentration of its aqueous solution and the equivalent conductance of the electrolyte at infinite dilution.*

$$\text{i.e. } \alpha = \frac{\wedge_c}{\wedge_o} \quad \dots 1.37$$

where  $\alpha$  = degree of dissociation

$\wedge_c$  = *equivalent conductance of the electrolyte at any specific concentration of solution of the electrolyte*

$\wedge_o$  = *equivalent conductance of the electrolyte at infinite dilution*

### Electronegativity and dissociation constant

When acetic acid is dissolved in water, the polar molecules of the water have a greater affinity for the hydrogen of acetic acid than for the acetate ion ( $CH_3COO^-$ ) has for the hydrogen to form again  $CH_3COOH$ . This difference in affinity leads to ionization of acetic acid to some extent in water because water has high electronegative oxygen and hence, it has more affinity for hydrogen ion.

Electronegativity increases the dissociation constant in the case of weak acids and it decreases the dissociation constant in the case of weak bases.

Introduction of chlorine atoms into acetic acid ( $CH_3COOH$ ) increases the ionization and hence, the acidity. Monochloroacetic acid ( $ClCH_2COOH$ ) is more acidic than acetic acid. This is

due to inductive effect (In inductive effect, the electrons of the molecule are attracted very strongly by highly electronegative atom such as chlorine atom) caused by highly electronegative chlorine atom which increases the dissociation constant. As a result, the bond between the hydrogen and oxygen in the carboxyl group (-COOH) is weakened. Hence, the degree of dissociation increases. Inclusion of more chlorine atoms to produce dichloroacetic acid ( $\text{Cl}_2\text{CHCOOH}$ ) and trichloroacetic acid ( $\text{Cl}_3\text{CCOOH}$ ) further increases the dissociation constant.

In the case of a weak base, substitution of chlorine atoms decreases the strength of the base.

### Ionic strength and dissociation constant

Ionic strength needs no consideration for solutions of non-electrolytes and for weak electrolytes present alone in solutions. In the case of weak electrolytes present alone in solution, the number of ions is small and the electrostatic forces are negligible. But in the case of weak electrolytes together with salts and other electrolytes such as those in buffered solutions, ionic strength is a factor to be considered.

Dissociation constant of a weakly acidic drug molecule is one of the most important properties as it can be related to physiologic and pharmacologic activities, solubility, rate of solution, extent of binding (i.e. protein binding) and rate of absorption of the drug. In the case of dilute solutions, the effect of ionic strength upon the acid-base equilibrium may be ignored. When stronger solutions or together with electrolytes are considered, the effect of ionic strength on dissociation constant must be considered. Most of the pharmaceutical solutions are in a concentration range where the ionic strength may influence the ionic equilibrium and observed dissociation constants.

$\text{pK}_a$  value refers to negative log of dissociation constant of the weak acid. This value may get altered by ionic strength. The altered value of  $\text{pK}_a$  is called as apparent  $\text{pK}_a$  or  $\text{pK}'_a$ . The apparent  $\text{pK}_a$  value is given by.

$$\text{pK}'_a = \text{pK}_a + \frac{0.51 (2Z-1)\sqrt{\mu}}{1 + \sqrt{\mu}} \quad \dots 1.38$$

where,  $\text{pK}_a$  = tabulated thermodynamic dissociation constant.

$Z$  = charge on the acid

$\mu$  = ionic strength

The ionic strength can be obtained from the equation given below.

$$\mu = \frac{1}{2} (C_1 Z_1^2 + C_2 Z_2^2 + \dots + C_n Z_n^2) \quad \dots 1.39$$

Where  $C$  is the concentration in moles per liter of the ionic species in solution and  $Z$  is the valence of the ion from the first one  $C_1$  to  $C_n$ <sup>th</sup> species.