STATES OF MATTER AND PHYSIOCHEMICAL PROPERTIES OF DRUG MOLECULES

Chapter Objectives

At the conclusion of this chapter the student should be able to:

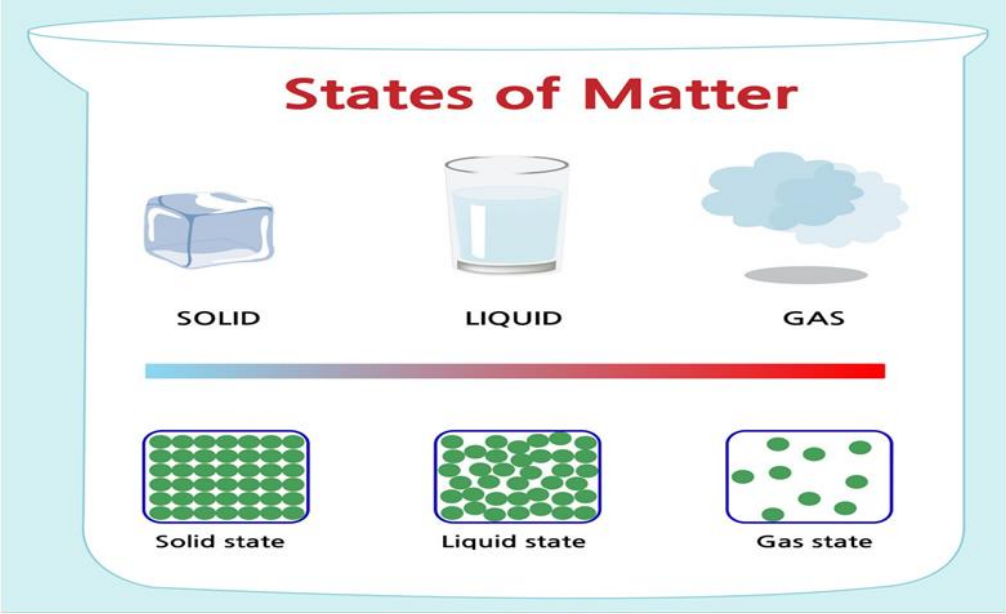
1. Differentiate between different types of states of matter and their main characteristics.
2. Know & understand the sublimation process and the types of mixtures.
3. Differentiate between different types of humidity systems and understand comparative study of their general properties.
4. Understand the main properties of solids and applications of these properties for the analysis of different solids.
5. Understand the main properties of refractive index, optical rotation, dielectric constant, dipole moment, dissociation constant and its applications.
6. Understand the main properties of different types of latent heats, vapour pressure and its applications.
7. Understand the main properties of aerosols, inhalers and its applications.

Subject: Physical Pharmaceutics – I **Unit No: I**
Faculty: M. MAHESHWAR **Lecture No: 1**
Topic: STATES OF MATTER **Book Reference: T1, T3**

STATES OF MATTER

Matter is a substance which occupies space and possess rest mass, especially as distinct from energy. Matters can be classified as

- Solid:(Ex-Tablet, capsule)
- Liquid:(Ex-Syrup, solution)
- Gas:(Ex-Aerosol)



Gases are compressible fluids. Their molecules are widely separated. Liquids are relatively incompressible fluids. Their molecules are more tightly packed. Solids are nearly incompressible and rigid. Their molecules or ions are in close contact and do not move. Comparison of Gases, Liquids and Solids In order for molecules to exist in aggregates in gases, liquids and solids Intermolecular forces must exist.

As two atoms or molecules are brought closer together, the opposite charges and binding forces in the two molecules are closer together than the similar charges and forces, causing the molecules to attract one another. The negatively charged electron clouds of molecules largely govern the balance (equilibrium) forces between the two molecules Repulsive and Attractive Forces.

CHANGES IN STATES OF MATTER

The following are the main changes that occur in the states of matter

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

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

Deposition: Deposition is a thermodynamic process, a phase transition in which gas transforms into solid without passing through the liquid phase. The reverse of deposition is sublimation and hence sometimes deposition is called de-sublimation. One example of deposition is the process by which, in sub-freezing air, water vapor changes directly to ice without first becoming a liquid. This is how snow forms in clouds, as well as how frost and hoar frost form on the ground or other surfaces.

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

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

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

Subject: Physical Pharmaceutics – I **Unit No: I**
Faculty: M. MAHESHWAR **Lecture No: 2**
Topic: SUBLIMATION CRITICAL POINT **Book Reference: T1, T3**

SUBLIMATION CRITICAL POINT

Sublimation is the change of state from a solid to a gas without passing through the liquid state. Carbon dioxide is an example of a material that easily undergoes sublimation. The temperature at which the vapor pressure of the solid phase of a compound is equal to the total pressure of the gas phase in contact with it; analogous to the boiling point of a liquid.

Phase Rule: Phase rule is a rule relating the possible numbers of phases, constituents, and degrees of freedom in a chemical system. This Rule was proposed by J. Willard Gibbs in 1876. The phase can he defined as any homogeneous part of a system having all the physical and chemical properties. The properties are identical throughout. A system may consist of one phase or more than one phase.

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

(2) A system containing liquid water and steam (a gas) is a two-phase or two-phase system

(P= 2).

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

$$P + F = C + 2$$

Where

P = number of phases that can coexist

F = number of components making up the phases, and

F= number of independent variables or degrees of freedom.

EUTECTIC MIXTURES

A eutectic mixture is defined as a mixture of two or more components which usually do not interact to form a new chemical compound but, which at certain ratios, inhibit the

crystallization process of one another resulting in a system having a lower melting point than either of the components. Eutectic mixtures, can be formed between Active Pharmaceutical Ingredients (APIs), between APIs and excipient or between excipient; thereby providing a vast scope for its applications in pharmaceutical industry.

Eutectic mixture formation is usually, governed by following factors:

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

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

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

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

Applications of Eutectic Mixtures in Pharmaceutical Industry

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

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

3. Eutectic mixtures are commonly used in drug designing and delivery processes for various routes of administration.

4. During manufacturing of pharmaceutical dosage form, it is extremely necessary to anticipate the formation of eutectics and avoid manufacturing problems if any. For example, during tablet compaction the heat produced in the punch and die cavities may lead to fusion or melting of tablet powder compacts leading to manufacturing defects. Thus, knowledge of eutectic points of powder components may help avoid these problems.

Subject: Physical Pharmaceutics – I **Unit No: I**
Faculty: M. MAHESHWAR **Lecture No: 3**
Topic: RELATIVE HUMIDITY **Book Reference: T1, T3**

RELATIVE HUMIDITY

Is a ratio, expressed in percent, of the amount of atmospheric moisture present relative to the amount that would be present if the air were saturated. Since the latter amount is dependent on temperature, relative humidity is a function of both moisture content and temperature. Relative Humidity is derived from the associated Temperature and Dew Point for the indicated hour.

LIQUID COMPLEXES

Complex fluids are binary mixtures that have a coexistence between two phases: solid–liquid (suspensions or solutions of macromolecules such as polymers), solid–gas (granular), liquid–gas (foams) or liquid–liquid (emulsions).

They exhibit unusual mechanical responses to applied stress or strain due to the geometrical constraints that the phase coexistence imposes. The mechanical response includes transitions between solid-like and fluid-like behaviour as well as fluctuations.

Their mechanical properties can be attributed to characteristics such as high disorder, caging, and clustering on multiple length scales. Shaving cream is an example of a complex fluid. Without stress, the foam appears to be a solid: it does not flow and can support (very) light loads. However, when adequate stress is applied, shaving cream flows easily like a fluid.

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

LIQUID CRYSTALS

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

Types of Liquid crystals: Liquid crystals are

A. **Thermotropic Liquid Crystals:** Liquid crystals are said to be thermotropic if liquid crystalline properties depend on the temperature.

a. Nematic Liquid Crystals: Here the molecules (mesogens) have no positional order, but they have long-range orientational order

b. Smectic Liquid Crystals: In this, the mesogens have both positional order and orientational order.

c. Cholesteric liquid Crystals: The cholesteric phase can be defined as a special type of nematic liquid crystals in which thin layers of the parallel mesogens have their longitudinal axes rotated in adjacent layers at certain angle.

B. **Lyotropic Liquid Crystals:** Liquid crystals which are prepared by mixing two or more substances of which one is a polar molecule, are known as lyotropic liquid crystals.

GLASSY STATES

The glassy state of materials refers to a nonequilibrium, solid state, such as is typical of inorganic glasses, synthetic non crystalline polymers and food components. Characteristics of the glassy state include transparency, solid appearance and brittleness. In such systems, molecules have no ordered structure and the volume of the system is larger than that of crystalline systems with the same composition. These systems are often referred to as

amorphous (i.e., disordered) solids (e.g., glass) or supercooled liquids (e.g., rubber, leather, syrup). Glasses are generally formed by melting crystalline materials at very high temperatures. When the melt cools, the atoms are enclosed in a random (disordered) state before they can form in a perfect crystalline arrangement.

Types: There are three types of glassy states-

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

The second type: It is consisting of organic glassy polymerization products. These glass in the stabilized state have fibrous structure of rigid valence bonded carbon atoms with small lateral branches in the form of hydrogen atoms or more complex radicals.

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

Subject: Physical Pharmaceutics – I **Unit No: I**
Faculty: M. MAHESHWAR **Lecture No: 4**
Topic: SOLID CRYSTALLINE STATE **Book Reference: T1, T3**

SOLID CRYSTALLINE STATE

A crystalline solid possesses rigid and long-range order. In a crystalline solid, atoms, molecules or ions occupy specific (predictable) positions.

Ionic Crystals

• Lattice points occupied by cations and anions

• Held together by electrostatic attraction

• Hard, brittle, high melting point

• Poor conductor of heat and electricity.

Metallic Crystals

• Lattice points occupied by metal atoms

• Held together by metallic bonds

• Soft to hard, low to high melting point

• Good conductors of heat and electricity.

Covalent Crystals

• Lattice points occupied by atoms

• Held together by covalent bonds

• Hard, high melting point

• Poor conductor of heat and electricity

AMORPHOUS SOLIDS

An amorphous solid does not possess a well-defined arrangement and long-range molecular order. Amorphous substances, as well as cubic crystal, are isotropic, that is, they exhibit similar properties in all direction. Solids that don't have a definite geometrical shape are known as Amorphous Solids.

1. In these solid particles are randomly arranged in three dimensions.

2. They don't have sharp melting points.

3. Amorphous solids are formed due to sudden cooling of liquid.

4. Amorphous solids melt over a wide range of temperature

POLYMORPHISM

Some elemental substance such as C and S, may exist in more than one crystalline form and are said to be allotropic, which is a special case of polymorphism. Polymorphism is the ability of a substance to exist in more than one crystal structure.

Polymorphs: when two crystals have the same chemical composition but different internal structure (molecular packing –molecular conformation or / and inter or intra molecular interactions) modifications or polymorphs or forms.

Pseudo polymorphs: different crystal forms have molecules of the same given substances and also contain molecules of solvent incorporated into a unique structure (solvates or hydrates).

The Principle of polymorphism: When the change from one form to another is reversible, it is said to be enantiotropic. When the transition takes place in one direction only—for example, from a metastable to a stable form—the change is said to be monotropic.

Subject: Physical Pharmaceutics – I **Unit No: I**
Faculty: M. MAHESHWAR **Lecture No: 5**
Topic: REFRACTIVE INDEX &OPTICAL ROTATION **Book Reference: T1, T3**

REFRACTIVE INDEX

The refractive index or index of refraction of a substance is a measure of the speed of light in that substance. It is expressed as a ratio of the speed of light in vacuum relative to that in the considered medium.

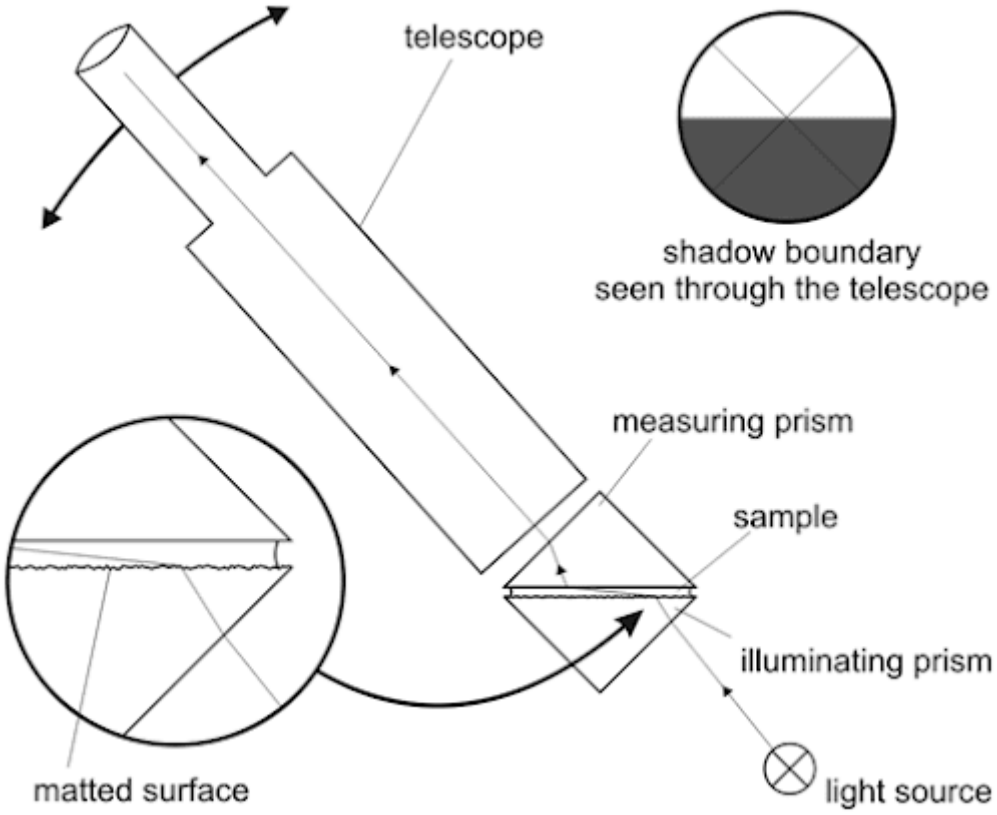
A simplified, mathematical description of refractive index is: n = velocity of light in a vacuum / velocity of light in medium Hence, the refractive index of water is 1.33, meaning that light travels 1.33 times as fast in a vacuum than it does in water.

The ratio of the sin i to sin r is constant. – This is called Snell's law. Laws of refraction Snell's law states that the ratio of the sines of the angles of incidence and refraction is equivalent to the ratio of velocities in the two media, or equivalent to the opposite ratio of the indices of refraction.

$$N = \frac{\sin i}{\sin r}$$

The instrument used to measure refractive index called Refractometer. Most common instrument is the Abbe Refractometer in which the liquid sample is sandwiched into a thin layer between an illuminating prism and a refracting prism.

The refracting prism is made of a glass with a high refractive index (e.g., 1.75) and the refractometer is designed to be used with samples having a refractive index smaller than that of the refracting prism.



ABBE'S REFRACTOMETER

Refractive index has the large number of applications. It is mostly applied for identify a particular substance, confirm its purity, or measure its concentration.

Generally, it is used to measure the concentration of a solute in an aqueous solution. For a solution of sugar, the refractive index can be used to determine the sugar content (Brix degree). It can be used also in determination of drug concentration in pharmaceutical industry.

It is used to calculate the focusing power of lenses, and the dispersive power of prisms. Also, it is applied for estimation of thermophysical properties of hydrocarbons and petroleum mixtures.

OPTICAL ROTATION

Optical rotation, also known as polarization rotation or circular birefringence, is the rotation of the orientation of the plane of polarization about the optical axis of linearly polarized light as it travels through certain materials. Circular birefringence and circular dichroism are the manifestations of optical activity.

Optical activity occurs only in chiral materials, those lacking microscopic mirror symmetry. Unlike other sources of birefringence which alter a beam's state of polarization, optical activity can be observed in fluids. This can include gases or solutions of chiral molecules such as sugars, molecules with helical secondary structure such as some proteins, and also chiral liquid crystals. It can also be observed in chiral solids such as certain crystals with a rotation between adjacent crystal planes (such as quartz) or metamaterials.

The rotation of the plane of polarization may be either clockwise, to the right (dextrorotary — d-rotary), or to the left (levorotary — l-rotary) depending on which stereoisomer is present (or dominant). For instance, sucrose and camphor are d-rotary whereas cholesterol is l-rotary. For a given substance, the angle by which the polarization of light of a specified wavelength is rotated is proportional to the path length through the material and (for a solution) proportional to its concentration.

When the polarized light passes through the optically active substance and rotates the plane of polarized light to the left side, or clockwise, then the compound is known as the dextrorotatory substance. If the rotation is observed in the right side, or anti-clockwise direction, then the compound is known as the laevorotatory substance.

The rotation of the plane polarized light is mainly based upon the asymmetric molecules and the steric configuration. The rotation is directly proportional to the concentration and the path length. The angle of rotation is calculated by Biot's formula:

$$\boldsymbol{\alpha = [\alpha]_D^{25} \times C \times d}$$

where C = concentration of the sample solution; d = path length of the sample cell; $[\alpha]_D^{25}$ = specific rotation of the sample at D line of the sodium at 25°C.

The optical activity is determined by the polarimeter which consists of the following components:

Source

Generally, sodium vapour lamp is employed. This produces wavelengths above 450 nm.

Filter

Filter is mainly used to polychromatic light into monochromatic light by absorbing the undesired radiation.

Sample Cell

Sample cells are long tubes which are made up of glass.

Analyzer

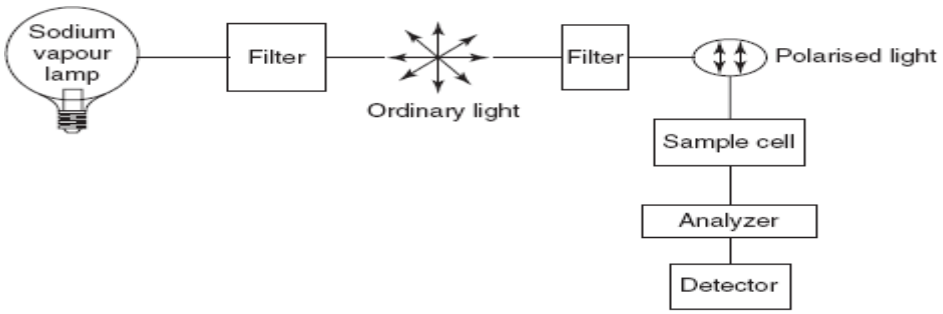
A nicol prism is used for this purpose. This is mainly used to analyze the samples whether they rotate the plane of polarized light on the right or left side.

Detector

The photomultiplier tube is commonly employed for the detection of the wavelength.

The procedure followed is sample tube filled with the sample solution which is placed between the polarizer and the analyzer. Then, allow the source of light to pass through the radiation. This ordinary light is polarized by the polarizer and the polarized light is passed through the sample solution. The optically active substance present in the sample solution rotates the plane polarized light into clockwise or in an anti-clockwise direction. Then, the analyzer measures the angle of rotation and is detected by the detector.

Optical activity is measured using a polarized source and polarimeter. This is a tool particularly used in the sugar industry to measure the sugar concentration of syrup, and generally in chemistry to measure the concentration or enantiomeric ratio of chiral molecules in solution. It is also used in the determination of the optical purity of substances.



POLARIMETER

Subject: Physical Pharmaceutics – I **Unit No: I**
Faculty: M. MAHESHWAR **Lecture No: 6**
Topic: DIELECTRIC CONSTANT & DIPOLEMOMENT **Book Reference: T1, T3**

DIELECTRIC CONSTANT

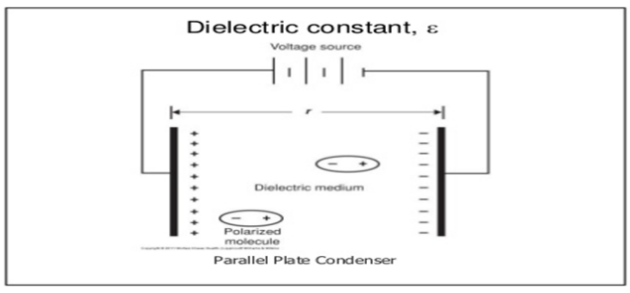
The relative permittivity, or dielectric constant, of a material is its (absolute) permittivity expressed as a ratio relative to the vacuum permittivity. Permittivity is a material property that affects the Coulomb force between two-point charges in the material. Relative permittivity is the factor by which the electric field between the charges is decreased relative to vacuum. Likewise, relative permittivity is the ratio of the capacitance of a capacitor using that material as a dielectric, compared with a similar capacitor that has vacuum as its dielectric.

Dielectric constant is the ratio of the capacitance formed by two plates with a material between them to the capacitance of the same plates with air as the dielectric. For low megahertz, frequencies are less than are equal to 1,000 MHz. For high megahertz, frequencies are greater than 1,000 MHz.

Relative permittivity is typically denoted as

$$\varepsilon(\omega) = \varepsilon / \varepsilon 0$$

where $\varepsilon(\omega)$ is the complex frequency-dependent permittivity of the material, and $\varepsilon 0$ is the vacuum permittivity.



The relative permittivity is an essential piece of information when designing capacitors, and in other circumstances where a material might be expected to introduce capacitance into a circuit. If a material with a high relative permittivity is placed in an electric field, the magnitude of that

field will be measurably reduced within the volume of the dielectric. This fact is commonly used to increase the capacitance of a particular capacitor design. The layers beneath etched conductors in printed circuit boards (PCBs) also act as dielectrics.

Dielectrics are used in RF transmission lines. In a coaxial cable, polyethylene can be used between the center conductor and outside shield. It can also be placed inside waveguides to form filters. Optical fibers are examples of dielectric waveguides. They consist of dielectric materials that are purposely doped with impurities so as to control the precise value of ε_r within the cross-section. This controls the refractive index of the material and therefore also the optical modes of transmission. However, in these cases it is technically the relative permittivity that matters, as they are not operated in the electrostatic limit.

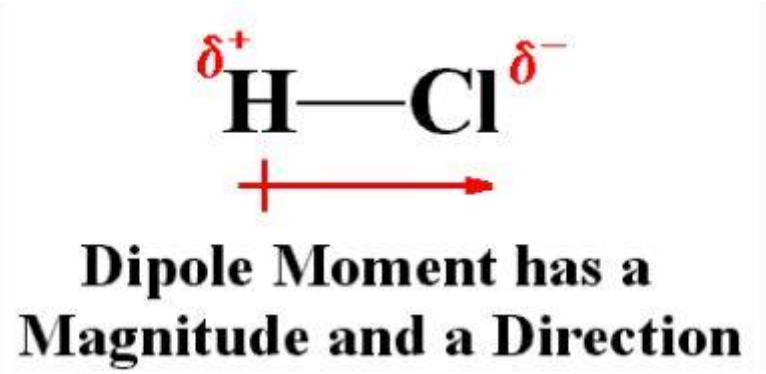
The relative permittivity of air changes with temperature, humidity, and barometric pressure. Sensors can be constructed to detect changes in capacitance caused by changes in the relative permittivity. Most of this change is due to effects of temperature and humidity as the barometric pressure is fairly stable. Using the capacitance change, along with the measured temperature, the relative humidity can be obtained using engineering formulas.

The relative static permittivity of a solvent is a relative measure of its chemical polarity. For example, water is very polar, and has a relative static permittivity of 80.10 at 20 °C while n-hexane is non-polar, and has a relative static permittivity of 1.89 at 20 °C. This information is important when designing separation, sample preparation and chromatography techniques in analytical chemistry.

DIPOLE MOMENT

A dipole moment arises in any system in which there is a separation of charge. They can, therefore, arise in ionic bonds as well as in covalent bonds. Dipole moments occur due to the difference in electronegativity between two chemically bonded atoms.

A bond dipole moment is a measure of the polarity of a chemical bond between two atoms in a molecule. It involves the concept of electric dipole moment, which is a measure of the separation of negative and positive charges in a system. The bond dipole moment is a vector quantity since it has both magnitude and direction. An illustration describing the dipole moment that arises in an HCl (hydrochloric acid) molecule is provided below.



It can be noted that the symbols $\delta+$ and $\delta-$ represent the two electric charges that arise in a molecule which are equal in magnitude but are of opposite signs. They are separated by a set distance, which is commonly denoted by 'd'.

The dipole moment of a single bond in a polyatomic molecule is known as the bond dipole moment and it is different from the dipole moment of the molecule as a whole. It is a vector quantity, i.e. it has magnitude as well as definite directions. Being a vector quantity, it can also be zero as the two oppositely acting bond dipoles can cancel each other. By convention, it is denoted by a small arrow with its tail on the negative center and its head on the positive center. In the case of a polyatomic molecule, the dipole moment of the molecule is the vector sum of the all present bond dipoles in the molecule. A dipole moment is the product of the magnitude of the charge and the distance between the centers of the positive and negative charges. It is denoted by the Greek letter 'μ'. Mathematically, Dipole Moment (μ) = Charge (Q) * distance of separation (r)

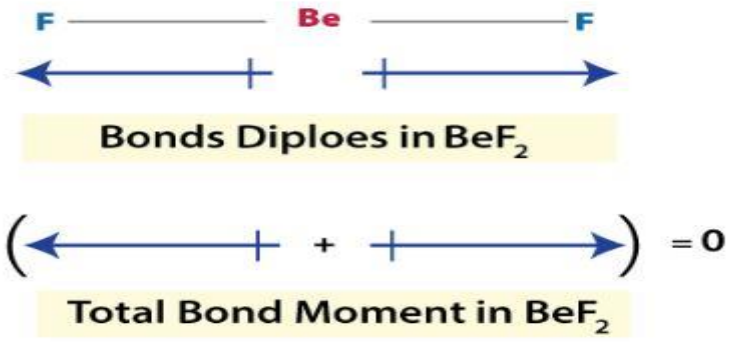
It is measured in Debye units denoted by 'D'. 1 D = 3.33564×10^{-30} C. m, where C is Coulomb and m denotes a meter. The bond dipole moment that arises in a chemical bond between two atoms of different electronegativities can be expressed as follows:

$$\mu = \delta \times d$$

Where: μ is the bond dipole moment, δ is the magnitude of the partial charges $\delta+$ and $\delta-$, And d is the distance between $\delta+$ and $\delta-$. The bond dipole moment (μ) is also a vector quantity, whose direction is parallel to the bond axis. In chemistry, the arrows that are drawn in order to represent dipole moments begin at the positive charge and end at the negative charge. When two atoms of varying electronegativities interact, the electrons tend to move from their initial positions to come closer to the more electronegative atom. This movement of electrons can be represented via the bond dipole moment.

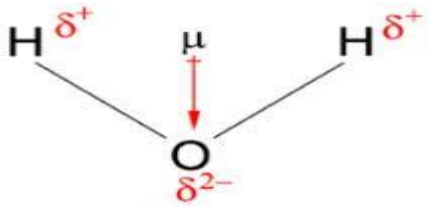
Dipole moment of BeF_2

In a beryllium fluoride molecule, the bond angle between the two beryllium-fluorine bonds is 180o. Fluorine, being the more electronegative atom, shifts the electron density towards itself. The individual bond dipole moments in a BeF2 molecule are illustrated below. From the illustration provided above, it can be understood that the two individual bond dipole moments cancel each other out in a BeF2 molecule because they are equal in magnitude but are opposite in direction. Therefore, the net dipole moment of a BeF2 molecule is zero.



Dipole moment of H2O (Water)

In a water molecule, the electrons are localized around the oxygen atom since it is much more electronegative than the hydrogen atom. However, the presence of a lone pair of electrons in the oxygen atom causes the water molecule to have a bent shape (as per the VSEPR theory). Therefore, the individual bond dipole moments do not cancel each other out as is the case in the BeF2 molecule. An illustration describing the dipole moment in a water molecule is provided below. The bond angle in a water molecule is 104.5o. The individual bond moment of an oxygen-hydrogen bond is 1.5 D. The net dipole moment in a water molecule is found to be 1.84D.



Subject: Physical Pharmaceutics – I **Unit No: I**
Faculty: M. MAHESHWAR **Lecture No: 7**
Topic: DISSOCIATION CONSTANT **Book Reference: T1, T3**

DISSOCIATION CONSTANT

The dissociation constant specifies the tendency of a substance M N to reversibly dissociate (separate) in a solution (often aqueous) into smaller components M and N:

$$Mx\ Ny(aq) + H2O(l) \rightleftharpoons xM(aq) + yN(aq)$$

The dissociation constant is denoted K_d and is calculated by

$$K_d = \frac{[M]x\ [N]y}{[Mx\ Ny]}$$

where A represents the activity of a species, and [M], [N], and [M N] are the molar concentrations of the entities M, N, and M N. Because water is the solvent, and the solution is assumed to be dilute, the water is assumed to be pure, and the activity of pure water is defined as 1. The activities of the solutes are approximated with molarities. The dissociation constant is an immediate consequence of the law of mass action which describes equilibria in a more general way. The dissociation constant is also sometimes called ionization constant when applied to salts. The inverse of the dissociation constant is called association constant.

Measure out about 0.2 g of the weak acid to be tested. For liquid acids, use about four drops. It is not necessary to know the exact amount. Measure precisely 50.0 mL of distilled water into a beaker, add the weak acid, stir to dissolve and mix well. If the acid does not readily dissolve, warm gently to dissolve, then cool to room temperature. Pour precisely 25.0 mL of the weak acid solution into an Erlenmeyer flask. Add 2 drops of phenolphthalein solution to the acid solution in the flask, and then add NaOH solution dropwise while swirling the flask. Stop adding the NaOH when the first pink colour persists throughout the solution. This process converts all of the weak acid, HA, in the flask into its conjugate base, A- , according to the neutralization reaction OH- + HA ◊ H2O + A- (one way arrow) At this point the beaker contains

exactly one-half of the original acid, essentially all of which is in the undissociated form, HA, and the flask contains an equal amount of the anion of the weak acid. Pour the contents of the flask into the beaker and mix the solution. Measure the pH of this solution using both a pH meter and pH indicator paper. The pH is the pKa of the acid. Calculate the value of Ka of the acid. The solutions may be washed down the drain with an excess of water.

The pKa value value indicates the strength of an acid in a specific solvent. This quantity is not only important for the classification of an acid, but also deter-mines the properties of a substance in nature or its possible use as a drug. The determination of the pKa value is there-fore of great importance in the pharmaceutical and agrochemical industries.

In drug research, synthesized compounds are screened for their ability to interact with specific target sites in biological entities such as enzymes, proteins, or cells. Only those compounds that show the desired biological activity, i.e. which are successfully absorbed and transferred to the target sites, are promising candidates for new drugs in medical therapy.

Almost all drug molecules form ionized species in aqueous solutions through the release of hydrogen ions H+. Due to the relationship between pKa and pH (see above), the pKa indicates which form of a drug molecule will exist at a given pH. In particular, the absorption of a drug molecule depends on the pH of the biological environment, on its nature (i.e. an aqueous or lipophilic environment) and on the structure of the drug molecule.

Subject: Physical Pharmaceutics – I **Unit No: I**
Faculty: M. MAHESHWAR **Lecture No: 8**
Topic: LATENT HEATS & VAPOR PRESSURE **Book Reference: T1, T3**

LATENT HEATS

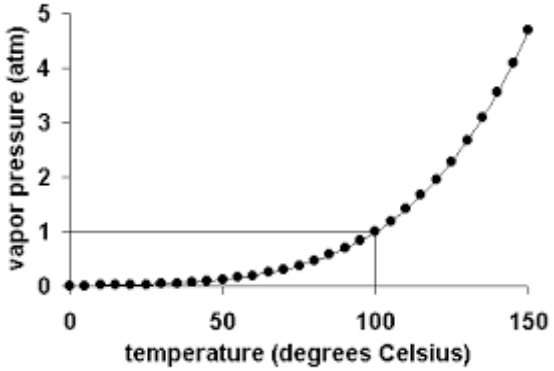
In Latent heat, energy absorbed or released by a substance during a change in its physical state (phase) that occurs without changing its temperature. The latent heat associated with melting a solid or freezing a liquid is called the heat of fusion; that associated with vaporizing a liquid or a solid or condensing a vapor is called the heat of vaporization.

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

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

VAPOR PRESSURE

The vapor pressure of a liquid is the equilibrium pressure of a vapor above its liquid (or solid); that is, the pressure of the vapor resulting from evaporation of a liquid (or solid) above a sample of the liquid (or solid) in a closed container. The vapor pressure of a liquid varies with its temperature, as the following graph shows for water. The line on the graph shows the boiling temperature for water.



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

Factors That Affect Vapor Pressure

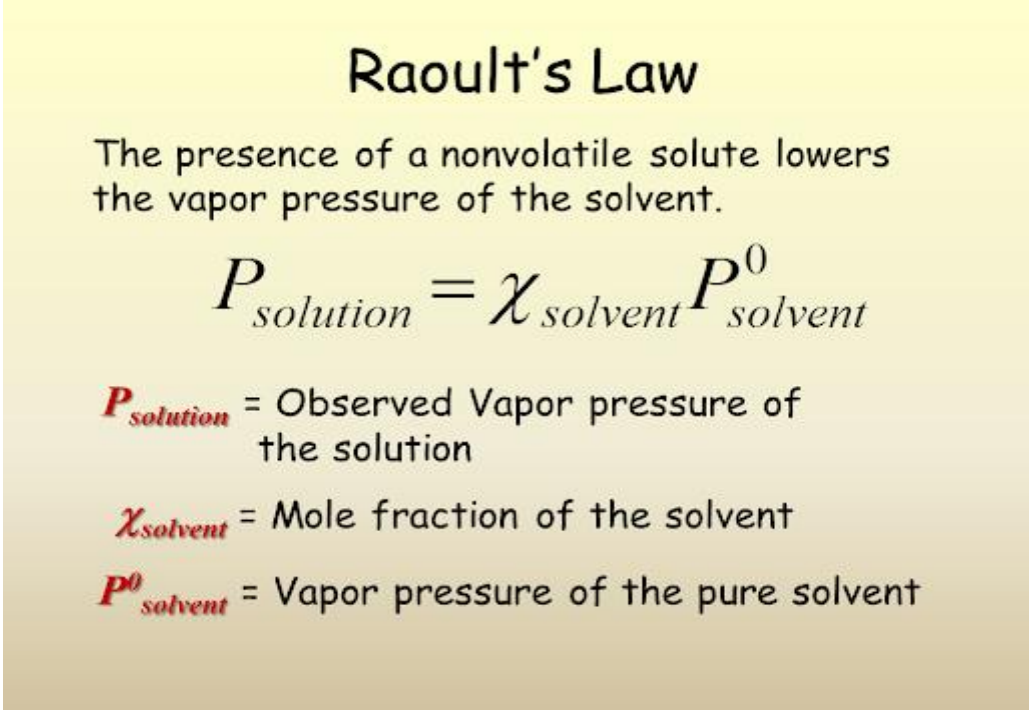
1. Surface Area: The vapor pressure is the equilibrium pressure where the rate of evaporation is equal to the rate of condensation. Since the scaling factor is the same, the vapor pressure is independent of the surface area.

2. Types of Molecules: the types of molecules that make up a solid or liquid determine its vapor pressure. If the intermolecular forces between molecules are: relatively strong, the vapor pressure will be relatively low. relatively weak, the vapor pressure will be relatively high.

3. Temperature: at a higher temperature, more molecules have enough energy to escape from the liquid or solid. At a lower temperature, fewer molecules have sufficient energy to escape from the liquid or solid.

4. Intermolecular Forces: Those liquids in which the intermolecular forces are weak shows high vapor pressure.

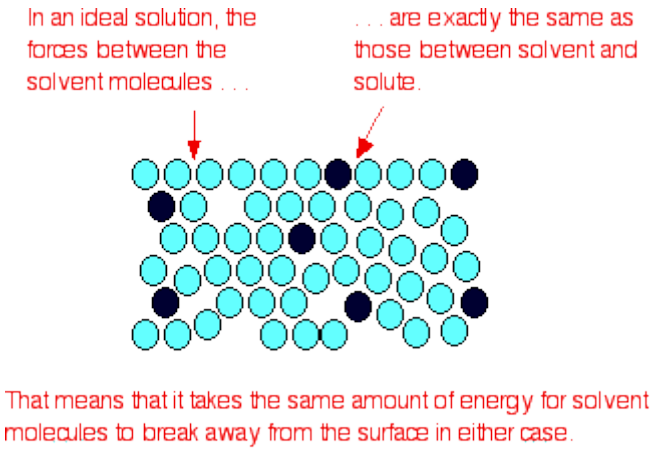
Raoult's law states that the vapor pressure of a solvent above a solution is *equal* to the vapor pressure of the pure solvent at the same temperature *scaled* by the mole fraction of the solvent present.



Limitations on Raoult's Law

In practice, there's no such thing as an ideal solution! However, features of one include:

- Ideal solutions satisfy Raoult's Law. The solution in the last diagram of Figure 33 above would not actually obey Raoult's Law - it is far too concentrated, but was drawn so concentrated to emphasized the point.
- In an ideal solution, it takes exactly the same amount of energy for a solvent molecule to break away from the surface of the solution as it did in the pure solvent. The forces of attraction between solvent and solute are exactly the same as between the original solvent molecules - not a very likely event!



Suppose that in the pure solvent, 1 in 1000 molecules had enough energy to overcome the intermolecular forces and break away from the surface in any given time. In an ideal solution, that would still be exactly the same proportion. Fewer would, of course, break away because there are now fewer solvent molecules on the surface - but of those that are on the surface, the same proportion still break away. If there were strong solvent-solute attractions, this proportion may be reduced to 1 in 2000, or 1 in 5000 or whatever.

In any real solution of, say, a salt in water, there are strong attractions between the water molecules and the ions. That would tend to slow down the loss of water molecules from the surface. However, if the solution is sufficiently dilute, there will be good-sized regions on the surface where you still have water molecules on their own. The solution will then approach ideal behaviour.

Subject: Physical Pharmaceutics – I **Unit No: I**
Faculty: M. MAHESHWAR **Lecture No: 9**
Topic: GASES, AEROSOLS & INHALERS **Book Reference: T1, T3**

GASES

Gases are compressible fluids. Their molecules are widely separated. As two atoms or molecules are brought closer together, the opposite charges and binding forces in the two molecules are closer together than the similar charges and forces, causing the molecules to attract one another.

The negatively charged electron clouds of molecules largely govern the balance (equilibrium) forces between the two molecules Repulsive and Attractive Forces.

Gas molecules travel in random paths and collide with one another and with the walls of the container in which they are confined A gas exerts a pressure (a force per unit area) expressed in dynes/cm2, atmospheres or in mmHg (1 atm = 760 mmHg = 760 Torr). Gases have volumes that is expressed in litres or cubic centimetres (1 cm3 = 1 mL).

The temperature involved in the gas equations is expressed by the absolute or Kelvin scale (0°C=273.15 K (Kelvin)).

Ideal gas is a gas where no intermolecular interactions exist and collisions are perfectly elastic, and thus no energy is exchanged during collision. The properties of the ideal gas can be described by the general ideal gas law, which are derived from Boyle, Charles and Gay-Lussac laws.

Boyle's law states that the volume and pressure of a given mass of gas is inversely proportional (i.e. when the pressure of a gas increases, its volume decreases). $P \alpha 1/V$ or $P = K/V$

$$P1V1 = P2V2$$

Where, P: pressure, K: constant, V: volume

Charles law states that the volume and absolute temperature of a given mass of gas at constant pressure are directly proportional (i.e. when the temperature of a gas increases, its volume increases as well). V α T or V=k T

V1 / T1 = V2 / T2

Where, T: temperature in Kelvin.

Gay-Lussac law states that the pressure and absolute temperature of a given mass of gas at constant volume are directly proportional (i.e. when the temperature of a gas increases, its pressure increases as well). P α T or P=k T

P1 / T1 = P2 / T2

Boyle, Gay-Lussac and Charles law can be combined to obtain the familiar relationship:

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

General ideal gas law (also called equation of state) relates the specific conditions, that is, the pressure, volume, and temperature of a given mass of gas.

PV/T = R

R: the molar gas constant value for the PV/T ratio of an ideal gas. For n moles it becomes:

PV = n RT

Kinetic molecular theory explains the behaviour of gases according to the ideal gas law:

1. Gases are composed of particles called atoms or molecules, the total volume of which is so small (negligible) in relation to the volume of the space in which the molecules are confined.
2. Gas molecules exert neither attractive nor repulsive forces on one another.

3.The particles exhibit continuous random motion. The average kinetic energy, E, is directly proportional to the absolute temperature of the gas, or E = (3/2) RT.

4. The molecules exhibit perfect elasticity; there is no net loss of speed or transfer of energy after they collide with one another and with the walls of the confining vessel.

AEROSOLS

Aerosol is a pressurized dosage forms containing one or more therapeutic active ingredients which upon actuation emit a fine dispersion of liquid and/or solid materials in a gaseous medium.

COMPONENTS OF AEROSOLS

1.PROPELLANTS

Responsible for developing proper pressure within the container. Provide driving force to expel the product from the container.

TYPES OF PROPELLANTS: (a) Liquefied gases Propellants (b) Compressed gases Propellants

LIQUEFIED GAS PROPELLANTS: Exist as liquids under pressure. Because the aerosol is under pressure propellant exists mainly as a liquid, but it will also be in the head space as a gas. The product is used up as the valve is opened, some of the liquid propellant turns to gas and keeps the head space full of gas. In this way the pressure in the can remains essentially constant and the spray performance is maintained.

Examples: Trichloromonofluoromethane - Propellant 11

Dichlorodifluoromethane - Propellant 12

Dichlorotetrafluoroethane - Propellant 114

COMPRESSED GAS PROPELLANTS: Compressed gas propellants occupy the head space above the liquid in the can. When the aerosol valve is opened the gas 'pushes' the liquid out of the can. The amount of gas in the headspace remains the same but it has more space, and as a result the pressure will drop during the life of the can. Spray performance is maintained however by careful choice of the aerosol valve and actuator.

Examples: Carbon dioxide, Nitrous oxide and Nitrogen

2.CONTAINERS

A. Metals 1. Tin plated steel 2. Aluminium 3. Stain less steel

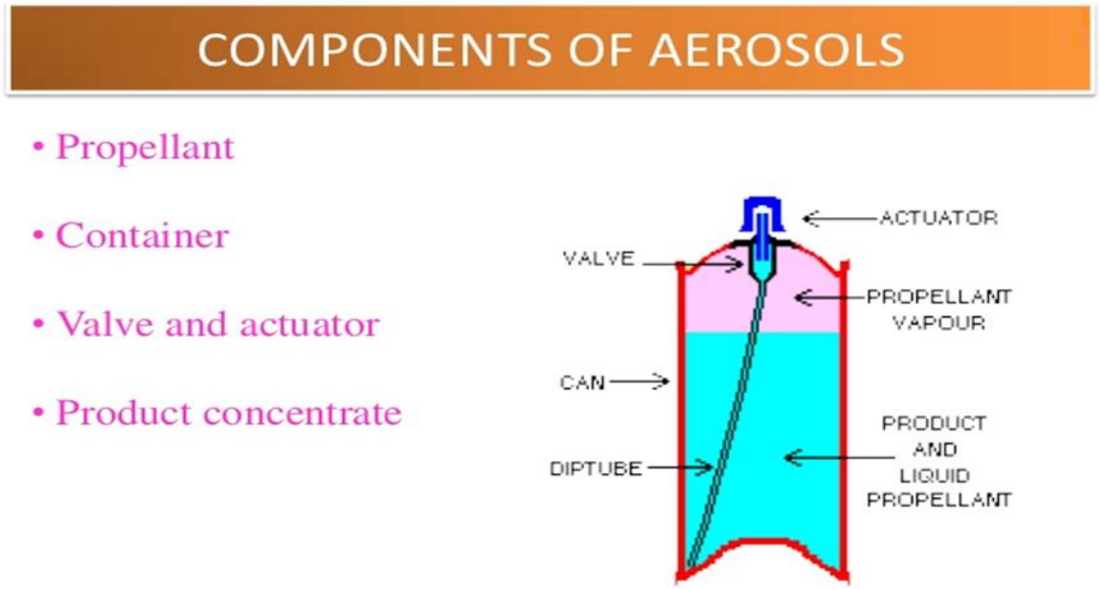
B. Glass 1. Uncoated glass 2. Plastic coated glass

3.VALVES

Easy to open and close. Capable of delivering the content in the desired form such as spray, foam, solid stream etc. It can deliver a given amount of medicament.

4.ACTUATORS

These are specially designed buttons which helps in delivering the drug in desired form i.e., spray, wet stream, foam or solid stream.



INHALERS

Types of pharmaceutical aerosols

Generally, pharmaceutical aerosols are stored in two types of inhalers viz., Metered-Dose Inhalers (MDIs) and Dry Powder Inhalers (DPIs). MDIs and DPIs deliver a specific quantity of drug to the lungs through pulmonary tracks on external surface of body parts. Both types of products are used to treat lung diseases characterized by obstruction of airflow and shortness of breath, including asthma and chronic obstructive pulmonary disease (COPD), as well as respiratory infections and cystic fibrosis. The inhalation route offers further potential for systemic drug delivery.

MDIs

The MDI is used to provide a certain dose of an aerosol of medication. It is likely to be either: Salbutamol/Ventolin (blue), Salmeterol/Serevent (green), or one that includes a small dose of steroid such as Fluticasone/Flixotide (orange), Seretide (purple), Becotide/Clenil (brown), Alvesco/Ciclesonide (red) or Fostair (pink). These work by relaxing the muscles of the large airways and/or reducing the inflammation of the airways.

Dry powder inhalers

Dry powder inhalers are an alternative to the aerosol-based inhalers commonly MDIs, that deliver a powder dosage form to the lungs. Most DPIs include an active ingredient and one or more excipient to aid powder dispersion and flow. The powder dose from a DPI can be analyzed on the PSA300 image analysis system. The optimum aerodynamic particle size distribution for most inhalation aerosols is very important and these are generally are in the range of 1-5 µm.

SOLUBILITY O F DRUGS

Chapter Objectives

At the conclusion of this chapter the student should be able to:

1. Know the different types of solubility expressions and their mechanisms.
2. Know & understand the ideal solubility parameters and process of solvation and association.
3. Differentiate between various types of factors of solubility and understand comparative study of their general properties
4. Understand the main properties of dissolution & drug release methods.
5. Understand the main properties of gases that are soluble in liquids.
6. Understand the main properties of liquids that are soluble in liquids and know the concept of ideal and real solutions.
7. Understand the main properties of azeotropic mixtures and method of fractional distillation.
8. Understand the main properties of partial miscible liquids, CST and its applications
9. Understand the concept of Distribution law, its limitations and applications
10. Understand the main properties of Diffusion principles in biological systems.

Subject: Physical Pharmaceutics-I **Unit No: II**
Faculty: M. MAHESHWAR **Lecture No: 1**
Topic: SOLUBILITY EXPRESSIONS **Book Reference: T1, T3**

SOLUBILITY EXPRESSIONS

Definitions

Solution is a mixture of two or more components that forms a single phase which is homogenous down to the molecular level.

Solvent(s)- Dissolves the solute. Determines the phase of solution. Usually constitute the largest proportion of the system.

Solute(s)- Dissolved in the solvent(s)- dispersed as molecules throughout the solvent. Usually constitute the smallest proportion of the system.

Dissolution- the transfer of molecules from a solid state into a solution.

Solubility- of a substance is the amount of the solute that passes into solution when the equilibrium is established. The solution that is obtained under these conditions is saturated.

Unsaturated- less than max. amount of solute dissolved in solvent.

Supersaturated- solutions that are formed by dissolving the solute to a level in excess of its solubility in a particular solvent with the aid of heat.

Expressions of Concentration:

Quantity per quantity- the weight or volume of solute that is contained in a given weight or volume of the solution. Eg:1gm/ml or 1gm/litre

Percentage- used with one of the four different meanings according to circumstances:

Percent % weight/weight, % weight/volume, % volume/volume and % volume/weight.

Parts- number of 'parts' of solute dissolved in a stated number of 'parts' of solution.

E.g.: parts per million and parts per billion.

Molarity- number of moles of solute dissolved in one litre of solution.

$$\text{Molarity(M)} = \frac{\text{number of moles}}{\text{Volume (litre)}}$$

Molality- number of moles of solute divided by the mass of the solvent.

$$\text{Molality(m)} = \frac{\text{number of moles}}{\text{Volume (kg)}}$$

Normality- number of moles of equivalents dissolved in one litre of solution.

$$\text{Normality} = \frac{\text{number of moles of equivalents}}{\text{Volume (litre)}}$$

Equivalent- mass (in gm)- It is equal to the amount of substance in moles divided by the valence of the substance.

For monovalent ions, 1 equivalent (Eq) = 1 mole, For divalent ions, 1Eq = 0.5 mole.

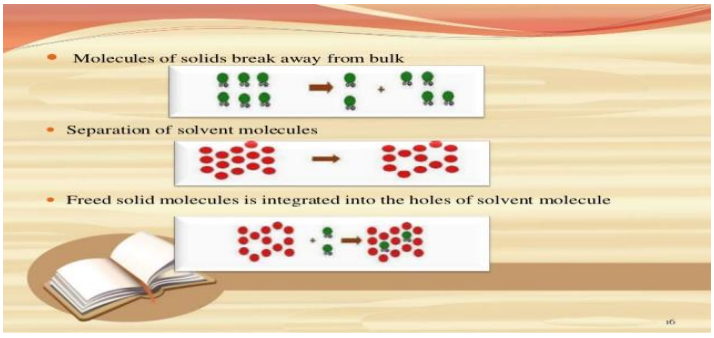
MECHANISM OF SOLUTE SOLVENT INTERACTION

The mechanism of solute solvent interaction involves following steps:

Breaking of inter-ionic or inter–molecular bonds in the solute. The separation of the molecules of the solvent to provide space in the solvent for the solute.

Interaction between the solvent and solute molecule or ion. Molecules of solids break away from bulk.

Separation of solvent molecules and freed solid molecules are integrated into the holes of solvent molecules.



Subject: Physical Pharmaceutics-I **Unit No: II**
Faculty: M. MAHESHWAR **Lecture No: 2**
Topic: IDEAL SOLUBILITY PARAMETER **Book Reference: T1, T3**

IDEAL SOLUBILITY PARAMETER

The Hildebrand solubility parameter (δ) provides a numerical estimate of the degree of interaction between materials and can be a good indication of solubility, particularly for nonpolar materials such as many polymers. Materials with similar values of δ are likely to be miscible.

The Hildebrand solubility parameter is the square root of the cohesive energy density:

$$\delta = \sqrt{((\Delta H_v - RT)/V_m)}$$

Where δ is Hildebrand solubility parameter,

ΔH_V is heat of vaporization,

R is gas constant,

T is temperature,

V_m is molar volume

The cohesive energy density is the amount of energy needed to completely remove unit volume of molecules from their neighbours to infinite separation (an ideal gas). This is equal to the heat of vaporization of the compound divided by its molar volume in the condensed phase. In order for a material to dissolve, these same interactions need to be overcome, as the molecules are separated from each other and surrounded by the solvent. In 1936 Joel Henry Hildebrand suggested the square root of the cohesive energy density as a numerical value indicating solvency behaviour. This later became known as the "Hildebrand solubility parameter".

Materials with similar solubility parameters will be able to interact with each other, resulting in solvation, miscibility or swelling.

SOLVATION AND ASSOCIATION

Solvation describes the interaction of solvent with dissolved molecules. Both ionized and uncharged molecules interact strongly with solvent, and the strength and nature of this interaction influence many properties of the solute, including solubility, reactivity, and colour, as well as influencing the properties of the solvent such as the viscosity and density. In the process of solvation, ions are surrounded by a concentric shell of solvent. Solvation is the process of reorganizing solvent and solute molecules into solvation complexes. Solvation involves bond formation, hydrogen bonding, and van der Waals forces. Solvation of a solute by water is called hydration.

Association is a chemical reaction whereby ions of opposite electrical charge come together in solution to form a distinct chemical entity. Ion associates are classified, according to the number of ions that associate with each other, as ion pairs, ion triplets, etc. Ion pairs are also classified according to the nature of the interaction as contact, solvent-shared or solvent-separated. Ions of opposite charge are naturally attracted to each other by the electrostatic force This is described by Coulomb's law:

$$F = \frac{q1\ q2}{\varepsilon\ r^2}$$

where F is the force of attraction, q_1 and q_2 are the magnitudes of the electrical charges, ε is the dielectric constant of the medium and r is the distance between the ions. For ions in solution this is an approximation because the ions exert a polarizing effect on the solvent molecules that surround them, which attenuates the electric field somewhat. Nevertheless, some general conclusions can be inferred.

Ion association will increase as:

- the magnitude(s) of the electrical charge(s) q_1 and q_2 increase,
- the magnitude of the dielectric constant ε decreases,
- the size of the ions decreases so that the distance r between cation and anion decreases.

Subject: Physical Pharmaceutics-I **Unit No: II**
Faculty: M. MAHESHWAR **Lecture No: 3**
Topic: FACTORS INFLUENCING SOLUBILITY OF DRUGS Book Reference: T1

FACTORS INFLUENCING SOLUBILITY OF DRUGS

The solubility of any drug or other components depends upon given points:

- Nature and composition of the solvent medium
- Physical form of the solid
- Temperature and pressure of system

1. Particle Size: The size of the solid particles affects the solubility because with the decrease in particle size, the surface area to volume ratio increases. The larger surface area of solute molecules allows more interaction with the solvent.

2. Molecular Size: The molecular size will affect the solubility of the drug as larger the molecule or higher the molecular weight of the drug, less is the solubility of that substance. In organic compounds, the amount of carbon branching increases the solubility because more branching will reduce the size of molecule and also make it easier for the solvent to solvate the molecules.

3. Temperature: With the increase in temperature the process of solution absorbs the energy and thus the solubility will get increased but if the process of solution releases the energy with the increase in temperature then it will decrease the solubility. Only a few solid solutes are there which are less soluble in warm solutions. In case of gases, the solubility get decreased when temperature of solution is increased.

4. Pressure: In case of solids and liquid solutes, there is no effect of pressure on the solubility but in case of gaseous solutes, when the pressure is enhanced, there is an increase in the solubility and with the decrease in pressure there is a decrease in solubility.

5. Nature of solute and solvent: There is a lot of difference in the solubility of two or more different substances on the basis of their natures. For example: In 100 grams of water at room temperature only 1 gram of Lead (II)chloride can be dissolved where 200 grams of Zinc

chloride can be dissolved in same amount of water i.e. 100 grams of water at same room temperature.

6. Polarity: The polarity of solute and the solvent molecules will affect the process of solubility. Generally, the polar solute molecules get dissolved in polar solvent system and nonpolar solute molecules get dissolved in nonpolar solvent system. Thus, if the solute molecule is polar in nature it must have both positive and negative ends and if the solvent is also of polar nature then it also consists of both the ends, thus the positive ends of solute molecule gets attracted towards the negative ends of the solvent molecules. These types of attractions are known as dipole-dipole interactions which is a type of intermolecular force.

7. Polymorphs: Solids have a rigid form and a definite shape. The shape or crystal habit of a given solid may vary but angles between the faces remains constant. A crystal is made up of ions, atoms or molecules in a lattice or in a regular geometric arrangement constantly repeated in three dimensions. This repeating arrangement is known as the unit cell. The ability of a substance to crystallize in more than one crystalline form is known s polymorphism. The polymorphs can vary in their melting points. As, the melting point of any solid is related to its solubility, the polymorphs will have different solubility.

8. Rate of solution: The rate of solution can be defined as the measure of how fast the substance dissolves in a solvent. The various factors that affect the rate of solution are:

- size of particles
- temperature
- amount of solute already dissolved
- stirring.

Subject: Physical Pharmaceutics-I **Unit No: II**
Faculty: M. MAHESHWAR **Lecture No: 4**
Topic: DISSOLUTION AND DRUG RELEASE **Book Reference: T1, T3**

DISSOLUTION AND DRUG RELEASE

Dissolution refers to the process by which a solid phase (e.g., a tablet or powder) goes into a solution phase such as water. It is the process for which drug molecules leave the boundary surrounding the dosage form and diffuses into the dissolution media.

Rate of dissolution is the amount of drug substance that goes in solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition. The rate of dissolution depends on:

• nature of the solvent and solute

• temperature (and to a small degree pressure)

• degree of under saturation

• presence of mixing

• interfacial surface area

• presence of inhibitors (e.g., a substance adsorbed on the surface).

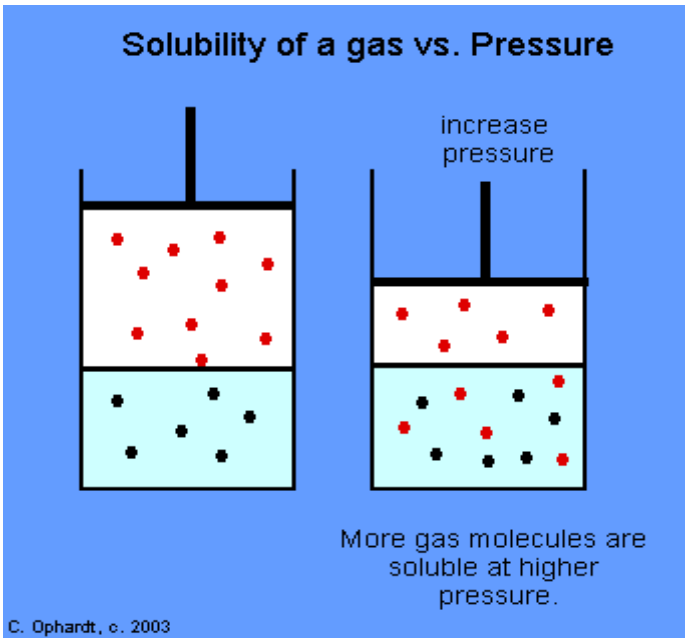
Drug release is the process by which a drug leaves a drug product. Immediate release drug products allow drugs to dissolve with no intention of delaying or prolonging dissolution or absorption of the drug. Delayed release is defined as the release of a drug at a time other than immediately following administration. (Enteric Coated). Enteric Coated: Intended to delay the release of the drug (or drugs) until the dosage form has passed through the stomach. Enteric-coated products are delayed-release dosage forms. Repeat action two single doses of medication; one for immediate release; another one for modified release.

Subject: Physical Pharmaceutics-I **Unit No: II**
Faculty: M. MAHESHWAR **Lecture No: 5**
Topic: SOLUBILITY OF GASES IN LIQUIDS **Book Reference: T1, T3**

SOLUBILITY OF GASES IN LIQUIDS

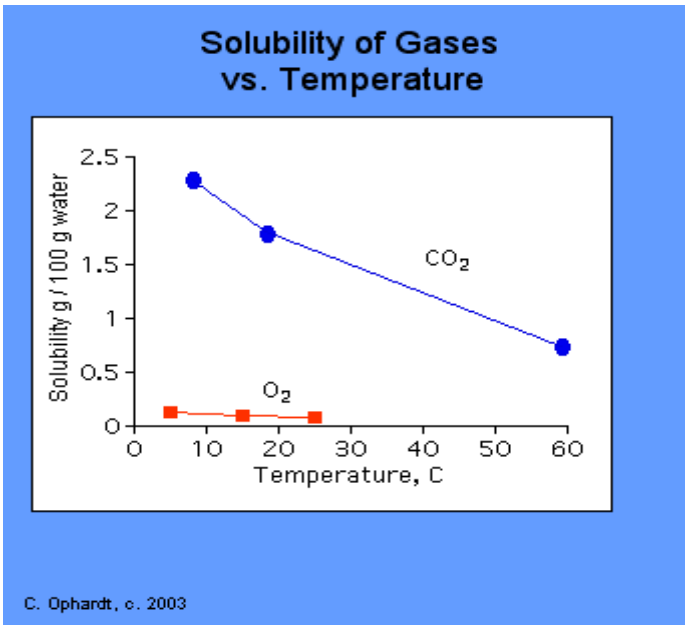
Henry's Law states that: The solubility of a gas in a liquid is directly proportional to the pressure of that gas above the surface of the solution.

If the pressure is increased, the gas molecules are "forced" into the solution since this will best relieve the pressure that has been applied. The number of gas molecules is decreased. The number of gas molecules dissolved in solution has increased as shown in the graph.



Carbonated beverages provide the best example of this phenomena. All carbonated beverages are bottled under pressure to increase the carbon dioxide dissolved in solution. When the bottle is opened, the pressure above the solution decreases. As a result, the solution effervesces and some of the carbon dioxide bubbles off.

As the temperature increases, the solubility of a gas decreases as shown by the downward trend in the graph.



More gas is present in a solution with a lower temperature compared to a solution with a higher temperature. The reason for this gas solubility relationship with temperature is very similar to the reason that vapor pressure increases with temperature. Increased temperature causes an increase in kinetic energy.

The higher kinetic energy causes more motion in molecules which break intermolecular bonds and escape from solution. This gas solubility relationship can be remembered if you think about what happens to a "soda pop" as it stands around for a while at room temperature. The taste is very "flat" since more of the "tangy" carbon dioxide bubbles have escaped. Boiled water also tastes "flat" because all of the oxygen gas has been removed by heating.

Subject: Physical Pharmaceutics-I **Unit No: II**
Faculty: M. MAHESHWAR **Lecture No: 6**
Topic: SOLUBILITY OF LIQUIDS IN LIQUIDS **Book Reference: T1, T3**

SOLUBILITY OF LIQUIDS IN LIQUIDS

The solubility of liquids in liquids includes as follows:

Showing complete miscibility e.g. water & ethyl alcohol

Showing complete immiscibility e.g. water & mercury

Showing partial miscibility e.g. water & phenol

The components of an ideal solution are miscible in all proportions. Such complete miscibility is also observed in some real binary systems, e.g. ethanol and water, under normal conditions. The attractions between the molecules of one component are greater than those between its molecules and those of the other component, i.e. if a positive deviation from Raoult's law occurs, the miscibility of the components may be reduced. The greater the strength of the self-association the greater the immiscibility the greater the degree of positive deviation from Raoults law. According to the Raoults law, 'the mole fraction of the solute component is directly proportional to its partial pressure'. On the basis of Raoult's Law, liquid-liquid solutions can be of two types. They are:

- Ideal Solutions
- Real Solutions

The solutions which obey Raoult's Law at every range of concentration and at all temperatures are Ideal Solutions. We can obtain ideal solutions by mixing two ideal components that are, solute and a solvent having similar molecular size and structure. For Example, consider two liquids A and B, and mix them. The formed solution will experience several intermolecular forces of attractions inside it, which will be:

A – A intermolecular forces of attraction

B – B intermolecular forces of attraction

A – B intermolecular forces of attraction

The solution is said to be an ideal solution, only when the intermolecular forces of attraction between A – A, B – B and A – B are nearly equal.

Examples of Ideal Solutions

- n-hexane and n-heptane
- Bromoethane and Chloroethane
- Benzene and Toluene
- CCl_4 and $SiCl_4$
- Chlorobenzene and Bromobenzene
- Ethyl Bromide and Ethyl Iodide
- n-Butyl Chloride and n-Butyl Bromide

The solutions which don't obey Raoult's law at every range of concentration and at all temperatures are real Solutions. These solutions deviate from ideal solutions and are also known as Non-Ideal Solutions.

Non-ideal solutions are of two types:

- Non-ideal solutions showing positive deviation from Raoult's Law
- Non-ideal solutions showing negative deviation from Raoult's Law

Positive Deviation from Raoult's Law

Positive Deviation from Raoult's Law occurs when the vapour pressure of the component is greater than what is expected in Raoult's Law. For Example, consider two components A and B to form non-ideal solutions. Let the vapour pressure, pure vapour pressure and mole fraction of component A be PA, PA0 and x A respectively and that of component B be PB, PB0 and x B respectively.

These liquids will show positive deviation when Raoult's Law when:

- $P_A > P_A^0 x_A$ and $P_B > P^0_B x_B$, as the total vapour pressure ($P_A^0 x_A + P^0_B x_B$) is greater than what it should be according to Raoult's Law.
- The solute-solvent forces of attraction are weaker than solute-solute and solvent-solvent interaction that is, A – B < A – A or B – B
- The enthalpy of mixing is positive that is, $\Delta_{mix} H > 0$ because the heat absorbed to form new molecular interaction is less than the heat released on breaking of original molecular interaction
- The volume of mixing is positive that is, $\Delta_{mix} V > 0$ as the volume expands on the dissolution of components A and B

Negative Deviation from Raoult's Law

Negative Deviation occurs when the total vapour pressure is less than what it should be according to Raoult's Law. Considering the same A and B components to form a non-ideal solution, it will show negative deviation from Raoult's Law only when:

- PA < PA0 xA and PB < P0B xB as the total vapour pressure (PA0 xA + P0B xB) is less than what it should be with respect to Raoult's Law
- The solute-solvent interaction is stronger than solute-solute and solvent-solvent interaction that is, A – B > A – A or B – B
- The enthalpy of mixing is negative that is, Δmix H < 0 because more heat is released when new molecular interactions are formed
- The volume of mixing is negative that is, Δmix V < 0 as the volume decreases on the dissolution of components A and B.

Examples of non-ideal Solutions

- Acetone and Carbon disulphide
- Acetone and Benzene
- Carbon Tetrachloride and Toluene or Chloroform
- Methyl Alcohol and Water
- Ethanol and Water

Subject: Physical Pharmaceutics-I **Unit No: II**
Faculty: M. MAHESHWAR **Lecture No: 7**
Topic: AZEOTROPIC MIXTURES **Book Reference: T1, T3**

AZEOTROPIC MIXTURES

Azeotropic mixtures are a mixture of at least two different liquids. Their mixture can either have a higher boiling point than either of the components or they can have a lower boiling point. Azeotropes occur when fraction of the liquids cannot be altered by distillation. Typically, when dealing with mixtures, components can be extracted out of solutions by means of Fractional Distillation, or essentially repeated distillation in stages (hence the idea of 'fractional'). The more volatile component tends to vaporize and is collected separately while the least volatile component remains in the distillation container and ultimately, the result is two pure, separate solutions.

Examples: Water and iso butanol, cyclohexane and benzene.

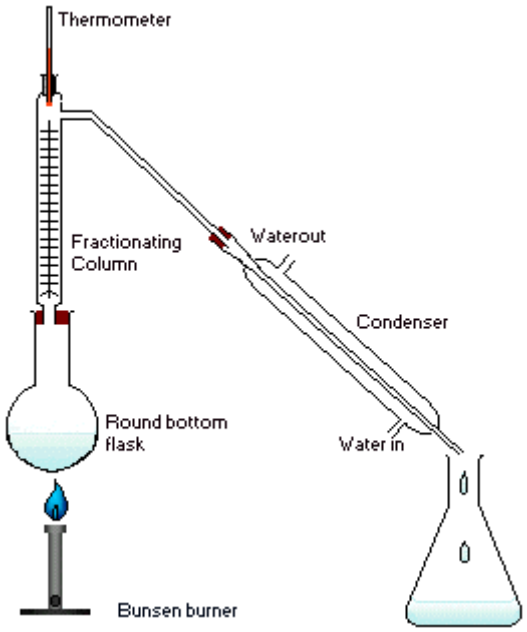
FRACTIONAL DISTILLATION

Fractional distillation is a type of distillation which involves the separation of miscible liquids. The process involves repeated distillations and condensations and the mixture is usually separated into component parts. The separation happens when the mixture is heated at a certain temperature where fractions of the mixture start to vaporize.

The basic principle of this type of distillation is that different liquids boil and evaporate at different temperatures. So, when the mixture is heated, the substance with lower boiling point starts to boil first and convert into vapors.

Fractional Distillation Procedure

Few fractional distillation apparatuses are required for the process. It includes distilling flask, condenser, receiver, fractionating column, thermometer and heat source.



After setting up the apparatus, a mixture of two miscible liquids A and B is taken where A has more volatility than substance B. The solution is added into the distilling flask while the fractionating column is connected at the tip of the flask. Heat is applied which increases the temperature slowly. The mixture then starts to boil and vapours start rising in the flask. The vapours are from the volatile component A. The vapours then start moving through the fractionating column into the condenser where it is cooled down to form a liquid which is collected in the receiver. Throughout the process, vaporization and condensation take place repeatedly until the two mixtures are separated completely.

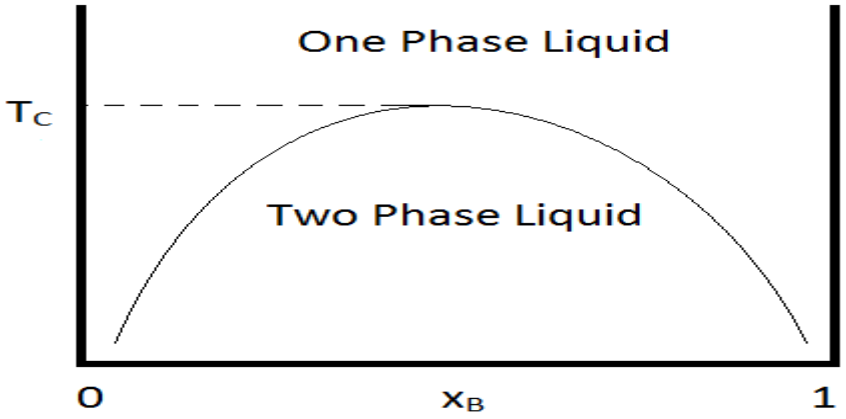
Applications of Fractional Distillation

- Fractional distillation is used for the purification of water as well as separating acetone and water.
- Fractional distillation is used in several industries like oil refineries and chemical plants mainly for purification and separation of many organic compounds.
- Fractional distillation is also used for the separation of (liquefied) air. Components like liquid nitrogen and oxygen as well as concentrated argon are obtained.
- Distillation is used in the production of high-purity silicon from chlorosilanes. The silicon is widely used in semiconductors.

Subject: Physical Pharmaceutics-I **Unit No: II**
Faculty: M. MAHESHWAR **Lecture No: 8**
Topic: PARTIALLY MISCIBLE LIQUIDS **Book Reference: T1, T3**

PARTIALLY MISCIBLE LIQUIDS

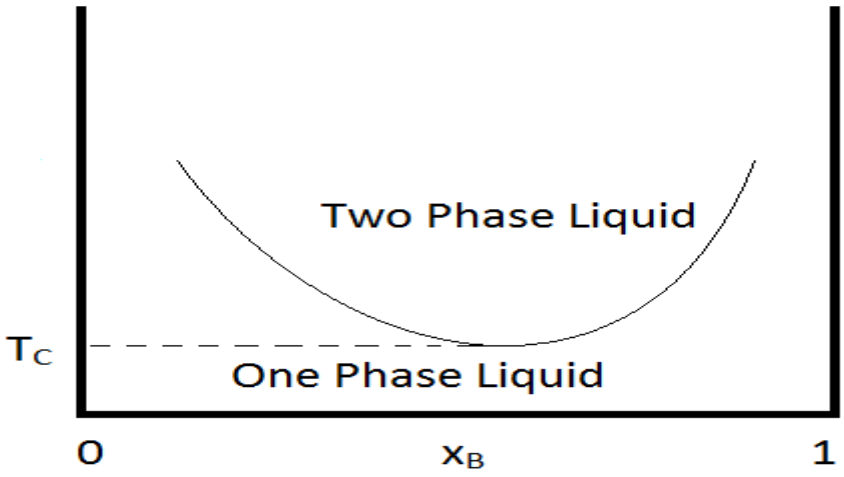
A pair of liquids is considered partially miscible if there is a set of compositions over which the liquids will form a two-phase liquid system. This is a common situation and is the general case for a pair of liquids where one is polar and the other non-polar (such as water and phenol). Another case that is commonly used that is the combination of diethyl ether and water. In this case, the differential solubility in the immiscible solvents allows the two-phase liquid system to be used to separate solutes using a separatory funnel method.



As is the case for most solutes, their solubility is dependent on temperature. For many binary mixtures of immiscible liquids, miscibility increases with increasing temperature. And then at some temperature (known as the upper critical temperature), the liquids become miscible in all compositions. An example of a phase diagram that demonstrates this behavior is shown in Figure. An example of a binary combination that shows this kind of behavior is that of phenol and water, for which the critical temperature is approximately 66.8 ^{0}C.

Another condition that can occur is for the two immiscible liquids to become completely miscible below a certain temperature, or to have a lower critical temperature. An example of a pair of compounds that show this behavior is water and trimethylamine. A typical phase

diagram for such a mixture is shown in Figure. Some combinations of substances show both an upper and lower critical temperature, forming two-phase liquid systems at temperatures between these two temperatures. An example of a combination of substances that demonstrate the behavior is nicotine and water.



CRITICAL SOLUTION TEMPERATURE

Phenol-water binary system is a system that shows the nature of the mutual solubility between phenol and water at a certain temperature and fixed pressure. When phenol and water are mixed together, two layers form which are:

a) the upper layer is a solution of water in phenol

b) the lower layer is a solution of phenol in water.

At a fixed temperature, the composition of each solution is fixed, and both the solutions are in equilibrium. Two solutions of different compositions existing in equilibrium with one another are known as conjugate solutions. Above a particular temperature, such solutions are completely miscible in all proportions. Such a temperature is known as the Critical Solution Temperature (CST) or Consolute Temperature. As the mutual solubility increases with temperature in this particular case, it is known as Upper Consolute Temperature. Above this temperature, the liquid mixture is homogeneous. Below this temperature, the mixture separates into two layers. Phenol and water are partially miscible at ordinary temperature. However, as the temperature is raised, the mutual solubility is increased. Phenol become then more soluble in water and water become more soluble in phenol. When a temperature reached between 65-

70°C, the liquids become completely miscible. The temperature at which this happen is called as the critical solution temperature.

Applications

To determine the purity of binary mixture samples.

To determine the composition of various samples of liquids in the mixtures.

Subject: Physical Pharmaceutics-I **Unit No: II**
Faculty: M. MAHESHWAR **Lecture No: 9**
Topic: DISTRIBUTION LAW **Book Reference: T1, T3**

DISTRIBUTION LAW

Distribution law or the Nernst's distribution law gives a generalization which governs the distribution of a solute between two non-miscible solvents. This law was first given by Nernst who studied the distribution of several solutes between different appropriate pairs of solvents.

C1/C2 = Kd

Where Kd is called the distribution coefficient or the partition coefficient. Concentration of X in solvent A/concentration of X in solvent B=Kd'

If C1 denotes the concentration of solute X in solvent A & C2 denotes the concentration of solute X in solvent B;

Nernst's distribution law can be expressed as C1/C2 = Kd. This law is only valid if the solute is in the same molecular form in both the solvents. Sometimes the solute dissociates or associates in the solvent.

Limitations of Distribution Law:

Stable temperature: The temperature is kept stable during the experiment.

Same molecular state: The law does not hold if there is an association or dissociation of the solute in one of the solvents. The molecular state of the solute has to stay stable when in make contact with the solvent. It should not endure dissociation or involvement.

Equilibrium concentrations: The concentrations of the solute are noted after the balance has been established.

Dilute solutions: The concentration of the solute in the two solvents is low. The law does not hold when the concentrations are high. The solute that is being dispersed shall not on ant situation imprudent towards the solvents being used.

Applications of Distribution Law

The distribution law can be applied to a number of physical and chemical processes. Thus, the association of the solute in one phase can be ascertained, and degree of association and therefore, the molecular mass of the solute in a given liquid can be found out. The law may also be used to determine the degree of dissociation of acids, bases or salts in a solvent.

The value of K is equal to the ratio of solubility of the solute in the two solvents. K =C1/C2 = S1/S2. If the value of K and solubility of the solute in one solvent is known then we can calculate the solubility of a solute in other solvents.

Extraction of one substance from a solution containing various substances by using a suitable solvent is known as solvent extraction. “The amount of extracted substance is more if a smaller amount of solvent is used many times rather than using a larger amount of solvent a fewer time”.

Subject: Physical Pharmaceutics-I **Unit No: II**
Faculty: M. MAHESHWAR **Lecture No: 10**
Topic: DIFFUSION PRINCIPLES **Book Reference: T1, T3**

DIFFUSION PRINCIPLES IN BIOLOGICAL SYSTEMS

Diffusion is a "Mass transfer of individual molecules of a substance caused by random molecular motion, associated with a driving force such as the concentration gradient" or " A physical process that refers to the net movement of molecules from a region of high concentration to lower concentration under the influence of concentration gradient."

Types of diffusion

Passive diffusion: The net moment of material from an area of high concentration to an area of low concentration. The difference between high and low concentration is termed as concentration gradient. Diffusion will continue until the gradient has been eliminated.

Facilitated (carrier mediated) diffusion: It is moment of molecules across the cell membrane via special transport proteins that are embedded within the cellular membrane. These are two types.

Active transport: Movement of molecules across a membrane from a region of lower concentration to higher concentration, against the concentration gradient.

Passive transport: Movement of molecules across a membrane from a region of higher concentration to lower concentration, along the concentration gradient.

FICK'S FIRST LAW OF DIFFUSION: "Diffusion flux is directly proportional to concentration gradient under the assumption of steady state diffusion"

$$J = -D \frac{dc}{dx}$$

Where, J= diffusion flux (g/ sq. cm/s)

D= Diffusion coefficient or diffusivity (cm sq./sec)

dc= change in concentration of material (g/cubic cm)

dx= change in distance (cm)

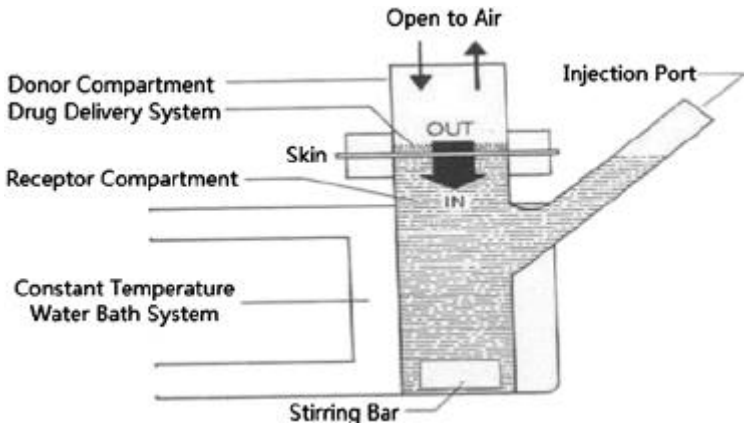
Diffusion flux (J) is mass transfer through a unit Cross section area in unit time.

FICK'S SECOND LAW OF DIFFUSION: "Change in concentration with time in a particular region is proportional to the change in concentration gradient at that point in the system."

$$dc/dt = -dJ/dx$$

MEASUREMENT OF DIFFUSION (Franz Diffusion cell)

Franz cell apparatus contain two chambers separated by a membrane. Donor chamber consist of known concentration of solute. Receptor chamber contain fluid from which samples are taken at a regular interval for analysis. Temperature is maintained at 37˚C. Membrane maybe of excised tissue, tissue constructs & cadaver tissue to synthetic membranes. When experiment starts, solute from donor chamber diffuses through membrane into receptor chamber. From receptor chamber, solution is periodically removed for analysis. The test determine amount of diffusant that has permeated the membrane. The solution of receptor chamber is replaced with new solution after each sampling.



FRANZ CELL

MICROMERETICS

Chapter Objectives

At the conclusion of this chapter the student should be able to:

1. Students are able to know the different types of particle sizes
2. Students are able to know & understand the properties of average particle size and weight distribution
3. Students are able to differentiate between different methods for particle size determination
4. Understand the main properties of counting and separation methods.
5. Understand the main properties of particle shape, specific surface.
6. Understand the main properties of permeability and adsorption methods.
7. Understand the concept of derived properties of powders.
8. Understand the main properties of porosity and packing
9. Understand the concept of flow properties of powder.
10. Understand the main properties of methods for determining surface area.

Subject: Physical Pharmaceutics-I **Unit No: III**
Faculty: M. MAHESHWAR **Lecture No: 1**
Topic: PARTICLE SIZE AND DISTRIBUTION **Book Reference: T1, T3**

PARTICLE SIZE AND DISTRIBUTION

Micromeritics is the study of fundamental and derived properties of individual as well as a collection of particles and thus can be called the science and technology of small particles. The particle size of a drug can affect its release from dosage forms that are administered orally, parenterally, rectally and topically. In the area of tablet and capsule manufacture, control of the particle size is essential in achieving the necessary flow properties and proper mixing of granules and powders.

PARTICLE SIZE AND DISTRIBUTION

Particle Size

In a collection of particles of more than one size, two properties are important, namely.

1. The shape and surface are of the individual particles.

2. The particle size and size distributions (The size range and number or weight of particles).

Size Distribution

When the number or weight of particles lying within a certain size range is plotted against the size range or mean particle size, a so-called frequency distribution curve is obtained. This is important because it is possible to have two samples with the same average diameter but different distributions.

RANGE OF PARTICLE SIZES

A guide to range of particle sizes applicable to each method is

Particle size	Method
1 μm	Electron microscope, ultracentrifuge, adsorption
1 — 100 μm	Optical microscope, sedimentation, coulter counter, air permeability
>50 μm	Sieving

Subject: Physical Pharmaceutics-I **Unit No: III**
Faculty: M. MAHESHWAR **Lecture No: 2**
Topic: PARTICLE SIZE AND WEIGHT DISTRIBUTION **Book Reference: T1, T3**

PARTICLE SIZE AND WEIGHT DISTRIBUTION

Particle Size

The size of a sphere is readily expressed in terms of its diameter.

The Surface diameter, d_s, is the diameter of a sphere having the same surface area as the particle.

The Volume diameter, d_v, is the diameter of a sphere having the same volume as the particle. The Projected diameter, d_p is the projected diameter of a sphere having the same observed area as the particle.

The Stokes diameter, d_{st}, is the diameter which describes an equivalent sphere undergoing sedimentation at the same rate as the asymmetric particle.

Any collection of particles is usually polydisperse. It is therefore necessary to know not only the size of a certain particle, but also how many particles of the same size exist in the sample. Thus, we need an estimate of the size range present and the number or weight fraction of each particle size. This is the particle-size distribution and from it we can calculate an average particle size for the sample.

Weight distribution

When the number or weight of particles lying within a certain size range is plotted against the size range or mean particle size, a so-called frequency distribution curve is obtained. This is important because it is possible to have two samples with the same average diameter but different distributions.

Subject: Physical Pharmaceutics-I **Unit No: III**
Faculty: M. MAHESHWAR **Lecture No: 3**
Topic: METHODS FOR DETERMINING PARTICLE SIZE **Book Reference: T1, T3**

METHODS FOR DETERMINING PARTICLE SIZE

Optical microscopy (1-150μm) or Electron microscopy (0.001μ-) Being able to examine each particle individually has led to microscopy being considered as an absolute measurement of particle size.

Can distinguish aggregates from single particles When coupled to image analysis computers each field can be examined, and a distribution obtained. Number distribution Most severe limitation of optical microscopy is the depth of focus being about 10μm at x100 and only 0.5μm at x1000.

With small particles, diffraction effects increase causing blurring at the edges - determination of particles < 3μm is less and less certain.

Advantages:

Relatively inexpensive

Each particle individually examined - detect aggregates, 2D shape, colour, melting point etc.

Small sample sizes required

Disadvantages

Time consuming - high operator fatigue - few particles examined

Very low throughput

No information on 3D shape

Certain amount of subjectivity associated with sizing - operator bias.

Sieving A sieve analysis (or gradation test) is a practice or procedure used (commonly used in civil engineering) to assess the particle size distribution (also called gradation) of a granular

material. The size distribution is often of critical importance to the way the material performs in use.

A sieve analysis can be performed on any type of non-organic or organic granular materials including sands, crushed rock, clays, granite, feldspars, coal, soil, a wide range of manufactured powders, grain and seeds, down to a minimum size depending on the exact method. Being such a simple technique of particle sizing, it is probably the most common.

Sieve analysis is performed using a nest or stack of sieves where each lower sieve has a smaller aperture size than that of the sieve above it. Sieves can be referred to either by their aperture size or by their mesh size (or sieve number).

The mesh size is the number of wires per linear inch. Approx. size range: 5µm - ~3mm Purpose This test is performed to determine the percentage of different grain sizes o contained within a soil. The mechanical or sieve analysis is performed to determine the distribution of the coarser, larger-sized particles, and the hydrometer method is used to determine the distribution of the finer particles.

Advantages:

Easy to perform

Wide size range

Inexpensive

Disadvantages

Known problems of reproducibility

Wear/damage in use or cleaning

Irregular/agglomerated particles

Rod-like particles: over estimate of under-size

Labour intensive

Sedimentation Technique: Methods depend on the fact that the terminal velocity of a particle in a fluid increases with size.

Stokes's Law:

$$D_{st} = \sqrt{\frac{18\mu V}{g(\rho_s - \rho_l)}}$$

Where,

Dst = Stokes' diameter

η = fluid viscosity

ρs = density of the solid

ρ1 = density of the liquid

V = settling velocity

g = acceleration due to gravity

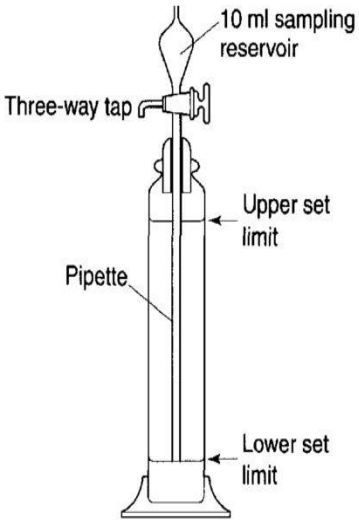
Stokes' diameter (D st) is defined as the diameter of the sphere that would settle at the same rate as the particle. The particle size distribution of fine powder can be determined by examining a sedimenting suspension of the powder.

(1) Incremental: changes with time in the concentration or density of the suspension at known depths are determined. Can be either fixed time or fixed depth techniques.

(2) Cumulative: the rate at which the powder is settling out of suspension is determined. i.e the accumulated particles are measured at a fixed level after all particles between it and the fluid's surface have settled.

Andreasen Pipette: Size distribution is determined by allowing a homogeneous suspension to settle in a cylinder and taking samples from the settling suspension at a fixed horizontal level at intervals of time.

Diagram of Andreasen pipette



Advantages:

Equipment required can be relatively simple and inexpensive.

Can measure a wide range of sizes with considerable accuracy and reproducibility.

Disadvantages

Sedimentation analyses must be carried out at concentrations which are sufficiently low for interactive effects between particles to be negligible so that their terminal falling velocities can be taken as equal to those of isolated particles.

Large particles create turbulence, are slowed and are recorded undersize.

Careful temperature control is necessary to suppress convection currents.

The lower limit of particle size is set by the increasing importance of Brownian motion for progressively smaller particles.

Particle re-aggregation during extended measurements.

Particles have to be completely insoluble in the suspending liquid.

Subject: Physical Pharmaceutics-I **Unit No: III**
Faculty: M. MAHESHWAR **Lecture No: 4**
Topic: PARTICLE COUNTING AND SEPARATION **Book Reference: T1, T3**

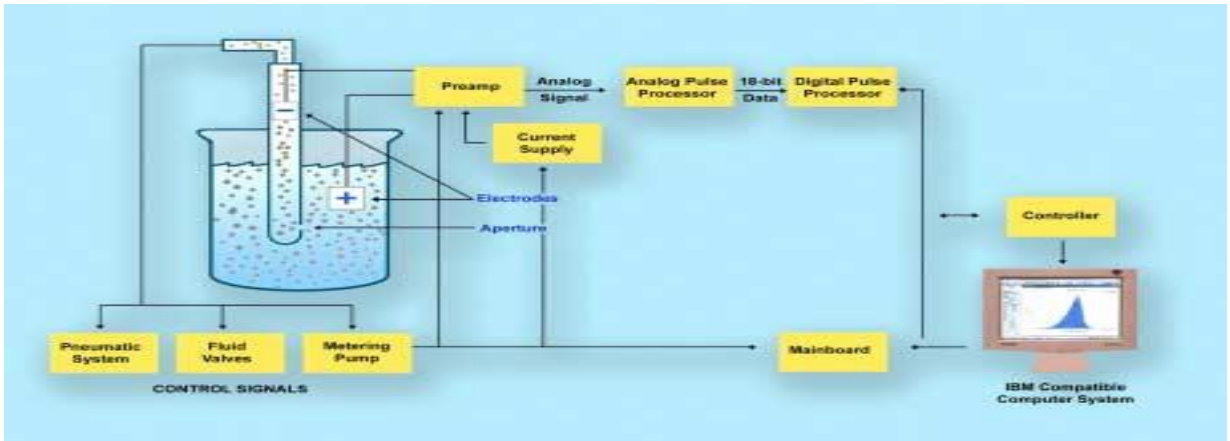
PARTICLE COUNTING AND SEPARATION

The Coulter Principle (Electrical Sensing Zone): Sizing and Counting of Particles

When an aperture is placed between two electrodes and a current path is offered by a low concentration electrolyte, resistance is determined between the electrodes. A sensing zone is formed. Low concentration particles suspended in electrolyte can be counted by passing them through the aperture. A volume of electrolyte equivalent to the immersed volume of the particle is displaced from the sensing zone.

This resistance change can be measured as a voltage pulse or a current pulse. The voltage pulse is proportional to the volume of the sensed particle. Using counter and pulse analyser circuits, the number and volume of particles passing through the sensing zone can be measured. The volume may be represented as the equivalent spherical diameter.

The measured particle sizes can be channelized using a height analyser circuit and a particle size distribution obtained. The electrical response of the instrument is essentially independent of the shape of particles with the same volume, an exception to this may occur with some extreme shapes. Colour or refractive index of the particles does not affect the results.



At the noise threshold the instantaneous concentration is determined for use by the concentration meter. This gives the user a means of checking the concentration of the sample. At the count threshold the number of pulses is counted using the same criterion as used for the

peak data. Thus, the count should be equal to the number of pulses stored in the peak buffer if the threshold was set equal to the count level.

Precautions:

The aperture tube used must be in the range 15 μm to 280μm diameter. The particle size distribution to be measured must be uni-modal, not exceeding approximately 2:1 by diameter in overall range and lie at a modal diameter which is less than approximately 15% of the aperture diameter to be used. The concentration of the particles should be less than approximately 10% aperture coincidence level.

Subject: Physical Pharmaceutics-I **Unit No: III**
Faculty: M. MAHESHWAR **Lecture No: 5**
Topic: PARTICLE SHAPE AND SPECIFIC SURFACE **Book Reference: T1, T3**

PARTICLE SHAPE AND SPECIFIC SURFACE

Particles are complex 3-dimensional objects and, as with particle size measurement, some simplification of the description of the particle is required in order to make measurement and data analysis feasible. Particle shape is most commonly measured using imaging techniques, where the data collected is a 2-dimensional projection of the particle profile. Particle shape parameters can be calculated from this 2-dimensional projection using simple geometrical calculations.

Particle form: The overall form of a particle can be characterized using relatively simple parameters such as aspect ratio. If we take as an example the image of the particle below, the aspect ratio can simply be defined as: **Aspect ratio =width/length.**

Aspect ratio can be used to distinguish between particles that have regular symmetry, such as spheres or cubes, and particles with different dimensions along one axis, such as needle shapes or ovoid particles. Other shape parameters that can be used to characterize particle form include elongation and roundness.

Particle outline: As well as detecting agglomerated particles, the outline of a particle can provide information about properties such as surface roughness. In order to calculate particle outline parameters, a concept known as the convex hull perimeter is used. In simple terms the convex hull perimeter is calculated from an imaginary elastic band which is stretched around the outline of the particle image.

Particles with very smooth outlines will have a convexity/solidity value close to one, whereas particles with rough outlines, or agglomerated primary particles, will have consequently lower convexity/solidity values.

Once the convex hull perimeter has been calculated we can then define parameters based upon it, such as convexity or solidity.

Where:

convexity = convex hull perimeter/actual perimeter

solidity = area bound by actual perimeter/area bound by convex hull perimeter.

The specific surface area of a particle is a function of porosity, pore size distribution, shape, size, and roughness. The role of the specific surface area is critical in the design of a heterogeneous catalyst where typically a domain with high specific surface area (e.g., γ-alumina, silica, zeolites) denominated carrier is included in the structure of the catalyst. An actual catalyst (e.g., platinum, rhodium, palladium) is deposited on the surface of the carrier to maximize the yield of the desired reaction and reduce the use of catalyst. Catalyst performance is therefore related with the specific surface area of the carrier.

A similar case is when substrates are used in absorption columns where the surface area of the particles used in the packed bed influences the yield and the time required to deactivate the column. Depending on the porosity and pore size distribution of the particle, the specific surface area is influenced by size, shape, and roughness.

When the particle structure presents nil or low porosity, the specific surface area of the particle is a function of these other attributes. Under these circumstances the specific surface area typically presents a stronger correlation with dissolution rate of the particle if the dissolution rate is controlled by external mass transfer.

The specific surface area is typically characterized by the physical adsorption of a gas (argon, krypton, or nitrogen) on the surface of the sample at cryogenic temperature. Gas adsorption can be determined by volumetric, gravimetric, or flux methods. The volume of gas adsorbed on a monolayer over the surface of the particles is determined according to the BET equation and the specific surface area is calculated based on molar volume of the gas and the average area occupied by the gas molecule.

Subject: Physical Pharmaceutics-I **Unit No: III**
Faculty: M. MAHESHWAR **Lecture No: 6**
Topic: PERMEABILITY AND ADSORPTION **Book Reference: T1, T3**

PERMEABILITY AND ADSORPTION

The permeability of a particle is a measure of how easily a fluid may flow through the pore channels in a solid. It depends on the size, shape, and number of the pore channels in the porous medium. Absolute permeability is the permeability of the porous medium if a single fluid is flowing. Effective permeability is the permeability of a fluid if another fluid is present. Relative permeability is the effective permeability divided by the absolute permeability.

Adsorption is the accumulation of a substance at a surface or interface. Absorption is the accumulation and distribution of a substance throughout a phase. Drugs are adsorbed by a membrane, enzyme or cell wall when they are attached to its surface. They are absorbed by a tissue, organ or blood when they permeate its entire bulk or volume.

Adsorption of material at solid interface may take place from either liquid or gas phase. The adsorption of gases at solid interface can be applied in the removal of odours, the operation of gas masks, and the measurement of the dimensions of particles as powders. The adsorption of liquids at solid interface can be applied in the decolorizing solutions, adsorption chromatography, detergency and wetting.

Subject: Physical Pharmaceutics-I **Unit No: III**
Faculty: M. MAHESHWAR **Lecture No: 7**
Topic: DERIVED PROPERTIES OF POWDERS **Book Reference: T1, T3**

DERIVED PROPERTIES OF POWDERS

Derived properties of powders include

Densities of Powders: It is defined as the mass per unit volume. There are three types of densities based on the determination method

True Density: The ratio of mass of the sample to the true volume is termed as true density of the sample. True density was determined with toluene displacement method. Powder sample (about 5 g) was submerged in toluene in a measuring cylinder having accuracy of 0.1 ml. The increase in liquid volume due to sample was noted as true volume of the sample which was then used to determine the true density of the sample (gm/cc).

$$\text{True Density} = \frac{\text{mass of the sample}}{\text{True volume of sample}}$$

Bulk Density: Pass the required quantity of powder through a sieve no: 20. Weigh the 10 gm of powder and place in 100 ml capacity of measuring cylinder. Fix the measuring cylinder to the bulk density apparatus and note the volume of the powder. Adjust the knob for 50 tapings and note the volume of the powder. Finally determine the bulk density (gm/cc) from the formula.

$$\text{Bulk Density} = \frac{\text{mass of the sample}}{\text{Bulk volume of sample}}$$

Bulkiness: The reciprocal of bulk density is known as the bulkiness or specific bulk volume. It increases with a decrease in particle size. It may get reduced since the smaller particles may shift between the larger ones.

Subject: Physical Pharmaceutics-I **Unit No: III**
Faculty: M. MAHESHWAR **Lecture No: 8**
Topic: POROSITY & PACKING ARRANGEMENT **Book Reference: T1, T3**

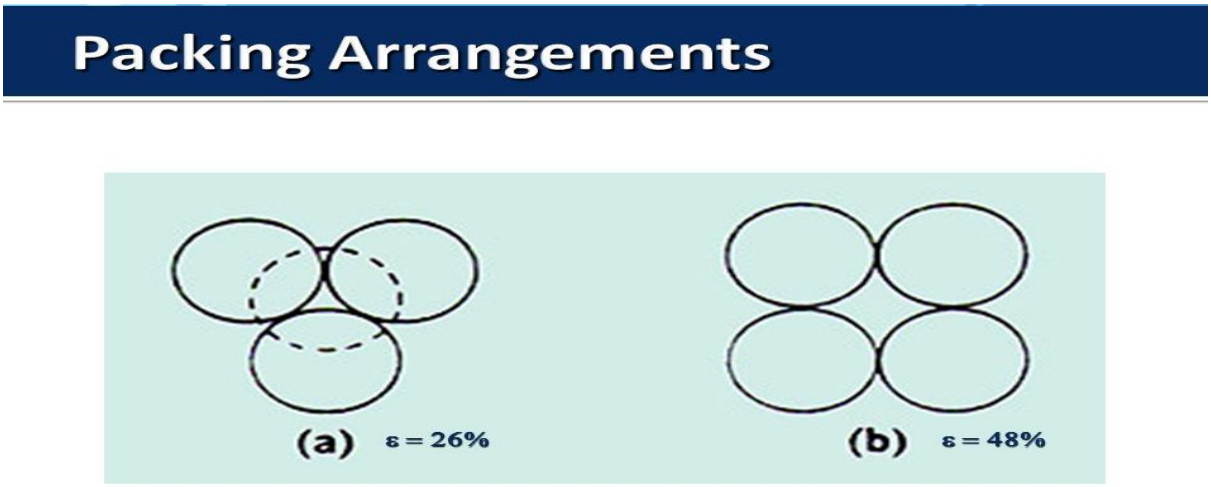
POROSITY & PACKING ARRANGEMENT

Porosity is defined as the fraction of the bulk volume V that is not occupied by solid matter. If the volume of solids is denoted by Vs, and the pore volume as Vp = V - Vs, we can write the porosity as

$$\Phi = \frac{V - Vs}{V} = \frac{\text{pore volume}}{\text{total bulk volume}}$$

The porosity can be expressed either as a fraction or as a percentage. Two out of the three terms are required to calculate porosity. It should be noted that the porosity does not give any information concerning pore sizes, their distribution, and their degree of connectivity.

Packing Arrangement of powder beds of uniform-sized spheres can assume either of two ideal packing arrangements: (a) closest or rhombohedral and (b)most open, loosest, or cubic packing. The theoretical porosity of a powder consisting of uniform spheres in closest packing is 26% and for loosest packing is 48%. The arrangements of spherical particles in closest and loosest packing.



The particles in real powders are neither spherical in shape nor uniform in size. It is to be expected that the particles of ordinary powders may have any arrangement intermediate between the two ideal packings and most powders in practice have porosities between 30% and

50%. If the particles are of greatly different sizes, however, the smaller ones may shift between the larger ones to give porosities below the theoretical minimum of 26%. In powders containing flocculates or aggregates, which lead to the formation of bridges and arches in the packing, the porosity may be above the theoretical maximum of 48%. In real powder systems, then, almost any degree of porosity is possible. Crystalline materials compressed under a force of 100,000 lb/in.2 can have porosities of less than 1%.

Subject: Physical Pharmaceutics-I **Unit No: III**
Faculty: M. MAHESHWAR **Lecture No: 9**
Topic: FLOW PROPERTIES OF POWDER **Book Reference: T1, T3**

FLOW PROPERTIES OF POWDER

A bulk powder is somewhat analogous to a non-Newtonian liquid, which exhibits plastic flow and sometimes dilatancy, the particles being influenced by attractive forces to varying degrees. Accordingly, powders may be free-flowing or cohesive ("sticky"). Of special significance are particle size, shape, porosity and density, and surface texture.

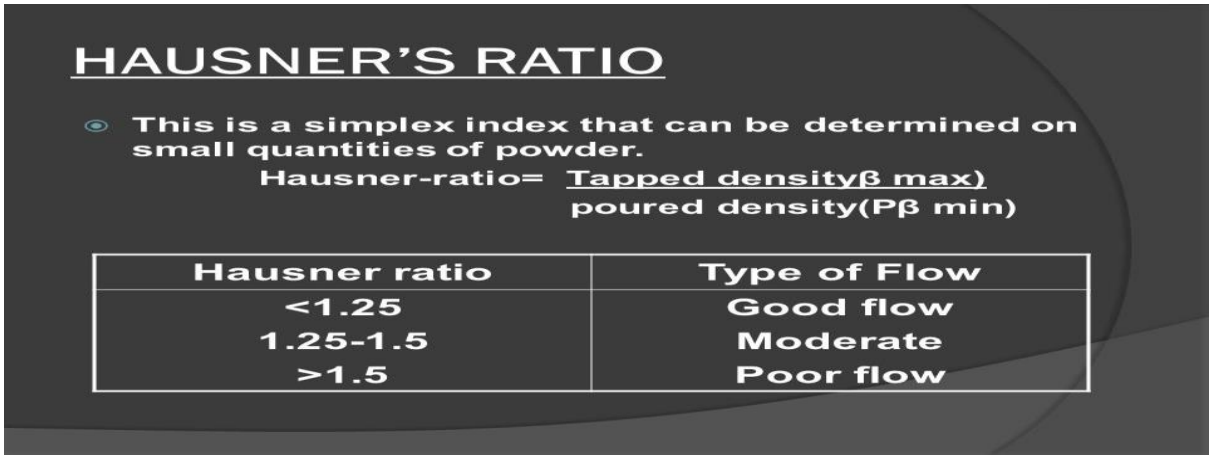
With relatively small particles (less than 10 μm), particle flow through an orifice is restricted because the cohesive forces between particles are of the same magnitude as gravitational forces. Because these latter forces are a function of the diameter raised to the third power, they become more significant as the particle size increases and flow is facilitated. A maximum flow rate is reached, after which the flow decreases as the size of the particles approaches that of the orifice.50 If a powder contains a reasonable number of small particles, the powder's flow properties may be improved be removing the "fines" or adsorbing them onto the larger particles. Occasionally, poor flow may result from the presence of moisture, in which case drying the particles will reduce the cohesiveness.

Carr's compressibility index: A volume of powder is filled into a graduated glass cylinder and repeatedly tapped for a known duration. The volume of powder after tapping is measured.

$$\text{Carr's index (\%)} = \frac{\text{Bulk density} - \text{Tapped density}}{\text{Tapped density}} \times 100$$

Carr's index (%)	Type of flow
≤10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very , Very poor

Hausner ratio was related to interparticle friction with value less than 1.25 indicates good flow. The powder with low interparticle friction, such as coarse spheres. Value greater than 1.5 indicates poor flow. More cohesive, less free-flowing powders such as flakes.



The angle of repose: The sample is poured onto the horizontal surface and the angle of the resulting pyramid is measured. The user normally selects the funnel orifice through which the powder flows slowly and reasonably constantly. The rougher and more irregular the surface of the particles, the higher will be the angle of repose.

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	> 66

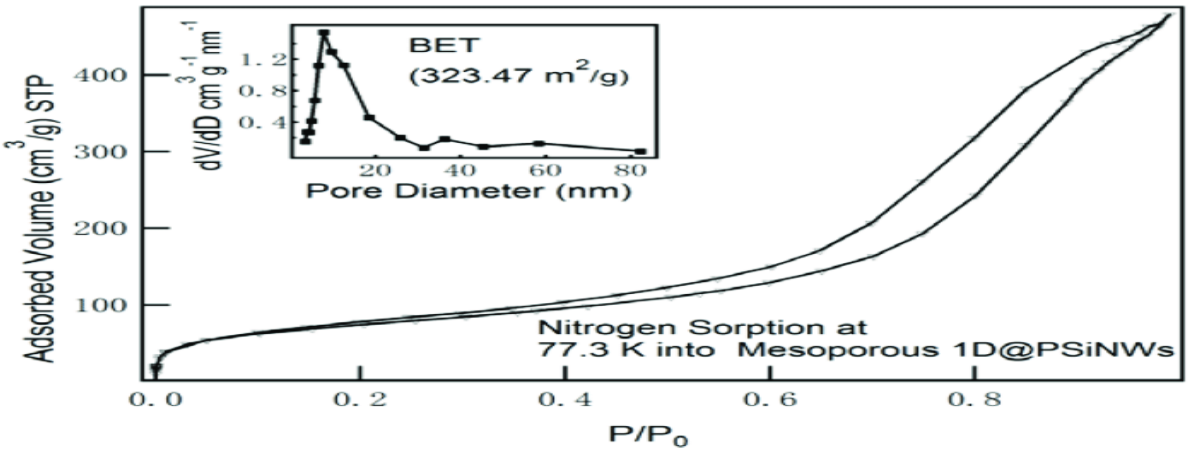
Subject: Physical Pharmaceutics-I **Unit No: III**
Faculty: M. MAHESHWAR **Lecture No: 10**
Topic: PARTICLE SURFACE AREA DETERMINATION **Book Reference: T1, T3**

PARTICLE SURFACE AREA DETERMINATION

The surface area of a powder sample can be computed from knowledge of the particle-size distribution obtained using one of the methods outlined previously. Two methods are commonly available that permit direct calculation of surface area. In the first, the amount of a gas or liquid solute that is adsorbed onto the sample of powder to form a monolayer is a direct function of the surface area of the sample. The second method depends on the fact that the rate at which a gas or liquid permeates a bed of powder is related, among other factors, to the surface area exposed to the permeant.

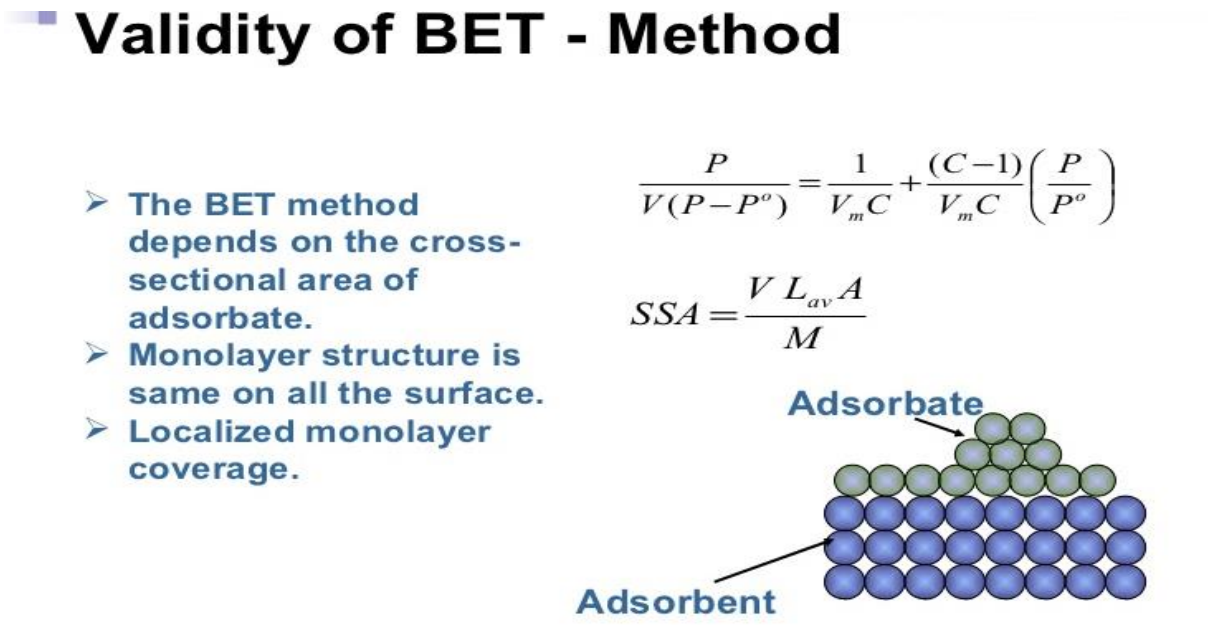
Adsorption Method

Particles with a large specific surface are good adsorbents for the adsorption of gases and of solutes from solution. In determining the surface of the adsorbent, the volume in cubic centimetres of gas adsorbed per gram of adsorbent can be plotted against the pressure of the gas at constant temperature to give a type II isotherms.



The adsorbed layer is monomolecular at low pressures and becomes multimolecular at higher pressures. The volume of nitrogen gas, Vm, in cm3 that 1 g of the powder can adsorb when the

monolayer is complete is more accurately given by using the Brunaver, Emmett, and Teller (BET) equation, which can be written as



where V is the volume of gas in cm3 adsorbed per gram of powder at pressure p, p0 is the saturation vapor pressure of liquefied nitrogen at the temperature of the experiment, and C is a constant that expresses the difference between the heat of adsorption and heat of liquefaction of the adsorbate.

Absorption and desorption of nitrogen gas on the powder sample is measured with a thermal conductivity detector when a mixture of helium and nitrogen is passed through a cell containing the powder. Nitrogen is the absorbate gas; helium is inert and is not adsorbed on the powder surface.

Emmett and Brunauer suggested that the value of Am for nitrogen be calculated from the formula,

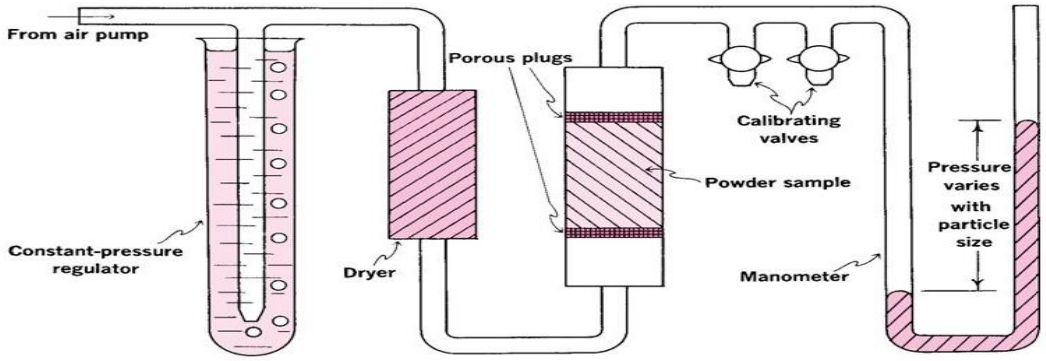
Am = 1.091{M / d N}

where M is the molecular weight, 28.01 g/mole, of N_2; d is the density, 0.81 g/cm3 of N_2 at its boiling point, 77 K (-196°C); and N is Avogadro's number. The quantity 1.091 is a packing factor for the nitrogen molecules on the surface of the adsorbent.

Air Permeability Method

The principal resistance to the flow of a fluid such as air through a plug of compacted powder is the surface area of the powder. The greater is the surface area per gram of powder, Sw, the greater is the resistance to flow. Hence, for a given pressure drop across the plug, permeability is inversely proportional to specific surface; measurement of the former provides a means of estimating this parameter.

Air Permeability Method



The Fisher subsieve sizer

A plug of powder can be regarded as a series of capillaries whose diameter is related to the average particle size. The internal surface of the capillaries is a function of the surface area of the particles. According to Poiseuille equation,

$$V = \frac{\pi d^4 \Delta P t}{128 l \eta}$$

where V is the volume of air flowing through a capillary of internal diameter d and length l in t seconds under a pressure difference of ΔP. The viscosity of the fluid (air) is η poise. In practice, the flow rate through the plug, or bed, is also affected by (a) the degree of compression of the particles and (b) the irregularity of the capillaries. The more compact the plug, the lower is the porosity, which is the ratio of the total space between the particles to the total volume of the plug. The irregularity of the capillaries means that they are longer than the length of the plug and are not circular.

COMPLEXATION AND PROTEIN BINDING

Chapter Objectives

At the conclusion of this chapter the student should be able to:

1. Students are able to know the concept of complexation
2. Students are able to know & understand the different types of complexes
3. Students are able to differentiate between different applications of complexation
4. Understand the main properties of complexation analysis methods.
5. Understand the main properties of protein binding
6. Understand the main properties of complexation and its drug action.
7. Understand the different crystalline structures of complexes.
8. Understand the main concept of stability constants treatment.

Subject: Physical Pharmaceutics-I **Unit No: IV**
Faculty: M. MAHESHWAR **Lecture No: 1**
Topic: INTRODUCTION TO COMPLEXATION **Book Reference: T1, T3**

INTRODUCTION TO COMPLEXATION

Complex compounds are defined as those molecules in which most of the bonding structures can be described by classical theories of valency between atoms, but one/more of these bonds are somewhat anomalous. Interaction between different chemical species Inter molecular forces Covalent bond Hydrogen bond Vander walls forces Ion-dipole, dipole-dipole, dipole-induced dipole complexes with different solubility, conductivity, partitioning, chemical reactions.

Complexes or coordination compounds, according to the classic definition, result from a donor–acceptor mechanism or Lewis acid–base reaction between two or more different chemical constituents. Any non-metallic atom or ion, whether free or contained in a neutral molecule or in an ionic compound, that can donate an electron pair can serve as the donor.

The acceptor, or constituent that accepts a share in the pair of electrons, is frequently a metallic ion, although it can be a neutral atom. Complexes can be divided broadly into two classes depending on whether the acceptor component is a metal ion or an organic molecule; these are classified according to one possible arrangement.

A third class, the inclusion/occlusion compounds, involving the entrapment of one compound in the molecular framework of another, is also included in the table. Intermolecular forces involved in the formation of complexes are the van der Waals forces of dispersion, dipolar, and induced dipolar types. Hydrogen bonding provides a significant force in some molecular complexes, and coordinate covalence is important in metal complexes.

Subject: Physical Pharmaceutics-I **Unit No: IV**
Faculty: M. MAHESHWAR **Lecture No: 2**
Topic: CLASSIFICATION OF COMPLEXES **Book Reference: T1, T3**

CLASSIFICATION OF COMPLEXES

Complexes are classified into

Metal complexes

1. Inorganic types 2. Chelates 3. Olefin type 4. Aromatic type

Organic molecular complexes

1. Drug-caffeine complex 2. Polymer type 3. Picric acid type 4. Quinhydrone type

Inclusion compounds

1. Channel type 2. Layer type 3. Clathrates 4. Mono molecular type

Metal complexes: METAL (substrate) Central atom base (ligand) Electron pair donor COMPLEX formed by co-ordination bond.

1. INORGANIC COMPLEXES:

Werner postulates:

1. There are two types of valences primary (ionic), secondary (coordinate).

2. Same type of anion/ radical/ molecule may be held by anyone / both type of valence.

3. Every central atom has fixed number of non-ionic valences (co- ordination number)

4. The co-ordination atoms occupy the first sphere/coordination sphere, other atoms occupy second/ ionization sphere.

5. Neutral molecules/ions may satisfy non-ionic valences.

6. The non-ionic valences are directed to specific positions in space. Ex: [Co Cl (NH3)5] Cl2 Substrate Coordination sphere Ionization sphere

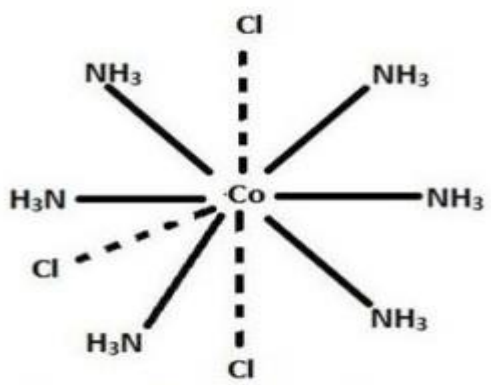


Fig.)$CoCl_3.6NH_3$ Complex
No of Cl- precipated =3
Total No of ions =4

[Co Cl (NH3)5] Cl2

1. Compound ionize to form [Co Cl (NH3)5]$^{+2}$ and 2Cl^{-}

2. Central chlorine do not precipitate with silver nitrate.

3. Substrate and ligand are bonded with coordination bond.

4. Coordination number is maximum number of atoms and groups that combine with central atom in coordination sphere.

5. Co-ordination number for cobalt is six.

2. CHELATES

These are group of metal ion complexes in which a substrate/ ligand provides two or more donor groups to combine with a metal ion. Ligands may be bidentate, tridentate, polydentate. Ex: Hexadentate - ethylenediaminetetraacetic acid (EDTA)- Has a total of six points (4:0 and 2: N) for attachment of metal ions.

Sequestering: This is a process in which the property of metal is suppressed without removing it from the solution. Sequestering Agent: This is a ligand which forms a stable water-soluble metal chelate Ex: chlorophyll, haemoglobin.

Chelates applications:

1. INCREASING SOLUBILITY: Fruit juices and drugs (ascorbic acid) + Fe/Cu oxidative degradation. Add EDTA + Fe/Cu stable Chelate

2. PURIFICATION OF HARD WATER: Hard water (Ca+2) + EDTA gives EDTA-Ca+2 (ppt) and filters to give pure water.

3. DURG ANALYSIS: Procainamide + cupric ions (1:1) at pH 4 to 4.5 gives coloured complex which is detected by Colourimetry.

4. ANTI-COAGULANT: Blood (Ca+2) + EDTA/Citrates/Oxalates prevents thrombin formation and there is no clotting.

3. OLEFIN AND AROMATIC TYPE:

These involves Lewis acid-base reactions and these types of complexes can be used as catalysts in the manufacturing of bulk drugs, intermediates and in drug analysis.

ORGANIC MOLECULAR COMPLEXES:

Interaction between two organic molecules forms Complex causes temperature change in molecular compound. These complexes have (H)bonds/ weak Vander wall forces/ dipole-induced dipole interactions. Energy of attraction is 3K. Cal/mole and Bond distance is three angstroms.

Complex Molecular compound Reaction in cold temperature Reaction in hot temperature. Weak attraction forces Strong electrostatic interactions Complexes cannot be separated from solutions Compounds can be separated from solutions.

PRINCIPLE/ MECHANISM:

1. Donor-Acceptor type: - Bonds between uncharged species is formed and stabilized by dipole-dipole interactions. EX: N-Dimethyl aniline + 2,4,6-Trinitro anisole.

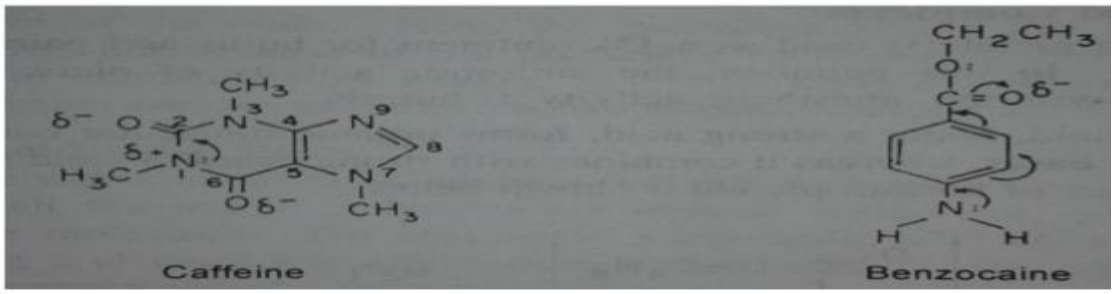
2. Charge transfer complexes: - One molecule polarizes other resulting in electrostatic interactions for complex formation with high inter molecular bonding. Complex is stabilized by resonance. Ex: Benzene + Trinitro benzene.

1. DRUG & CAFFINE COMPLEX:

Acidic drugs (benzocaine, procaine) reacts with Caffeine and form Complexes

Mechanism:

1. dipole-dipole forces/ hydrogen bonding between acid (H) atom and caffeine carboxyl group.
2. Interaction of non-polar parts Ex: Caffeine + Benzocaine.



Applications:

1. These complexes can improve or extend absorption and bioavailability of drug.

2. These complexes can enhance or inhibit solubility and dissolution rate of drug.

3. Caffeine with gentisic acid complexes mask bitter taste of caffeine.

2. POLYMER COMPLEXES

Polymers with nucleophilic oxygen (PEG/CMC) and Drugs (tannic acid/salicylic acid/phenols) form complexes.

Disadvantages:

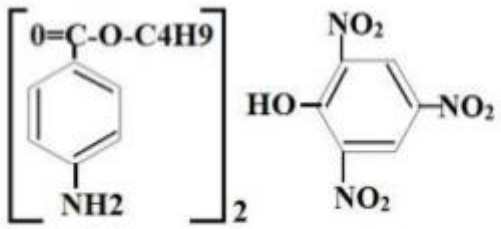
1. Incompatibilities in suspension, emulsion, ointments.

2. Complexes with Container drug loss

3. Complexes and preservatives decrease preservative action.

3. PICRIC ACID COMPLEXES

Picric acid (strong acid) reacts with strong base and forms Salt of Picric acid (strong acid) and also reacts with weak base. Ex: Butesin picrate is formed by complexation of Picric acid (antiseptic) and Butesin (anaesthetic) which is 1% ointment used for burns and abrasions.

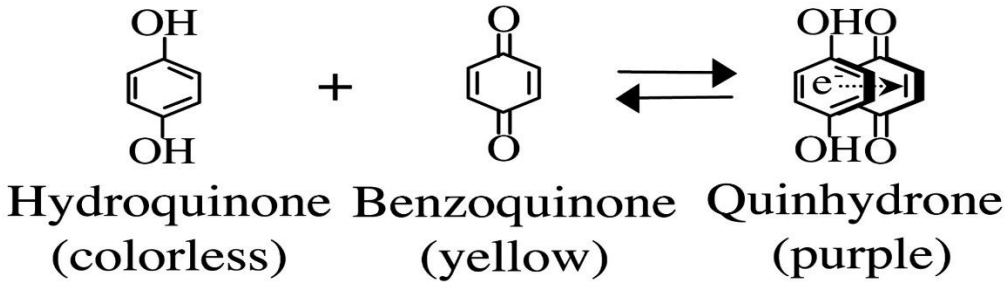


BUTESIN PICRATE

DISADVANTAGES: Picric acid and Carcinogenic Agents form complex to increase carcinogenic activity.

4. QUINHYDRONE COMPLEXES

Alcoholic solutions of equimolar quantities of Hydroquinone and Benzoquinone form Quinhydrone complexes (green crystals)



Mechanism:

1. Overlapping of π electrons of molecules

2. Hydrogen bonding for stabilizing complex.

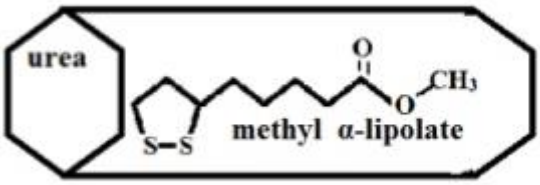
Applications: Used as electrode in pH determination.

INCLUSION COMPLEXES OR OCCLUSION COMPOUNDS

One compound is trapped in lattice/cage like structure of another compound. Interaction are due to suitable molecular structure. Prediction of complex formation is difficult.

1. **CHANNEL LATTICE TYPE**

The host (tubular channel)- Deoxycholic acid, urea, thiourea, amylose gives space for guest (long unbranched straight chain compounds)- paraffin, esters, acids, ethanol. Ex: Starch-iodine solution (starch-host), Urea-methyl α-lipolate (urea-host).



Urea-methyl α-lipolate (urea-host)

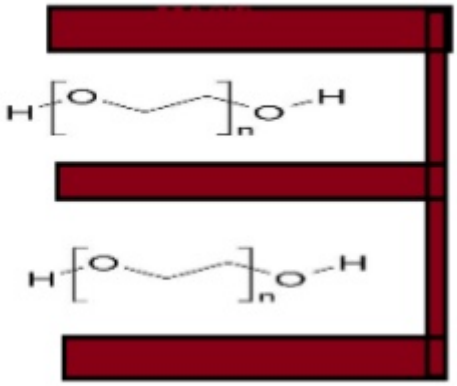
Applications:

Separation of isomers: Dextro, levo-terpineol are separated using Digitoxin.

In analysis of dermatological creams, long chain compounds interfere and removed by complexation with urea.

2. LAYER TYPES

The Host (Layers with Gaps)- clays, bentonite, montmorillite are entrapped with guest (entrapped in gaps)- hydrocarbons, alcohols, glycols.

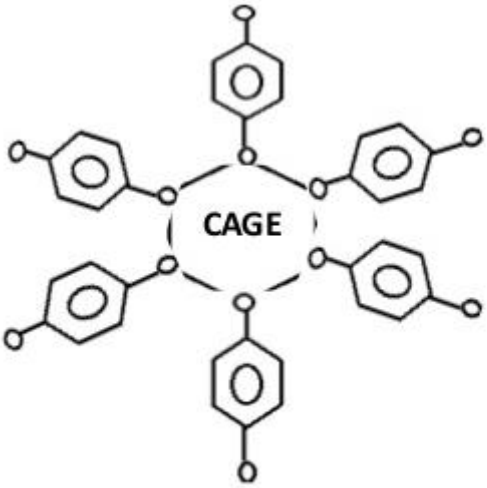


LAYER TYPE COMPLEX

Use: Due to their large surface area they are used as catalysts.

3. CLATHRATES

These are (cage like structure) during crystallization of some compounds (host) form cage like structures in which coordinating compound (guest) is entrapped.



CLATHRATES

Ex: warfarin sodium (water + isopropyl alcohol) Hydroquinone form cage with hydrogen bonds and hole have diameter of 4.2A0. This can entrap methanol, carbon dioxide, hydrochloric acid.

APPLICATIONS:

1. Synthetic metalo- alumino silicates act as molecular sieves.

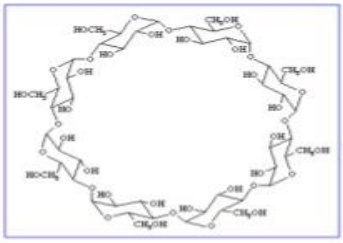
2. The pores store volatile gases and toxic substances.

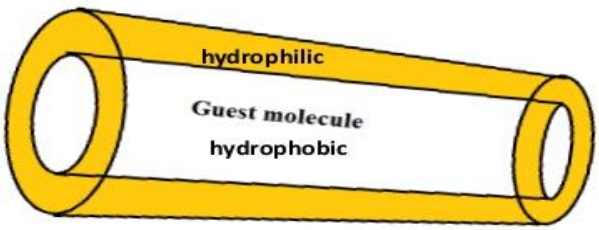
3. The entrapped molecule can be removed by physical process.

4. MONO MOLECULAR INCLUSION COMPLEX

Single guest molecule entrapped by single host molecule. HOST- Cyclodextrins. Cyclodextrins are cyclic oligo saccharides containing minimum of 6 D- glucose pyranose units attached by α-1,4 linkages.

Cyclodextrins	Cavity diameter (A°)	Glucopyranose units
α	5	6
β	6	7
γ	8	8





APPLICATIONS:

1. Enhanced solubility: Retonic acid has solubility of 0.5mg/ml that combines with β-Cyclodextrin increase solubility up to 160 mg/ml.

2. Enhanced dissolution: Famotidine/ Tolbutamide with β-Cyclodextrin

3. Enhanced stability: Aspirin/Ephedrine/Testosterone with β-Cyclodextrin (no reaction with other functional groups)

Subject: Physical Pharmaceutics-I **Unit No: IV**
Faculty: M. MAHESHWAR **Lecture No: 3**
Topic: APPLICATIONS OF COMPLEXATION **Book Reference: T1, T3**

APPLICATIONS OF COMPLEXATION

Applications in pharmacy

Physical state: Liquid substance along with Solid complex improve process characteristics. Ex: Nitro-glycerine (Explosive) with β-Cyclodextrin becomes explosion proof Complex

Volatility: The substances with complex nature reduce volatility (volatile / unpleasant odour) & Mask odour

Solid state stability: Vitamin-A, D when combines with β-Cyclodextrin forms chemically stable solid complex.

Chemical stability: Complexation reduce reactivity and improve stability. Ex: Caffeine and Benzocaine Complex prevent benzocaine hydrolysis.

Solubility: The insoluble PABA forms complexation with Caffeine to form complex improves solubility of PABA.

Dissolution: Phenobarbitol combines with β-Cyclodextrin that forms complex and improves Solubility & Dissolution.

Reduced Toxicity: β-Cyclodextrin reacts with Indomethacin that reduce ulcerogenic effect and reduce local tissue toxicity.

Antidote in metal poisoning: Dimercaprol reacts with arsenic and mercury that forms complex and easily eliminates Mercury from body.

Drug action through metal poisoning: 8-Hydroxy Quinoline forms iron complex that enter into malarial parasite shows Anti-Malarial action.

Subject: Physical Pharmaceutics-I **Unit No: IV**
Faculty: M. MAHESHWAR **Lecture No: 4**
Topic: ANALYSIS OF COMPLEXATION **Book Reference: T1, T3**

ANALYSIS OF COMPLEXATION

A determination of the stoichiometric ratio of ligand to metal or donor to acceptor (n) and a quantitative expression of the stability constant for complex formation are important in the study and application of coordination compounds.

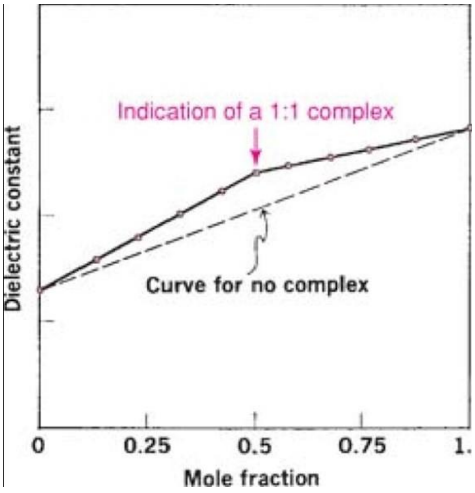
Method of Continuous Variation: Job suggested the use of an additive property such as the spectrophotometric extinction coefficient (dielectric constant or the square of the refractive index may also be used) for the measurement of complexation.

If the property for two species is sufficiently different and if no interaction occurs when the components are mixed, then the value of the property is the weighted mean of the values of the separate species in the mixture.

This means that if the additive property, say dielectric constant, is plotted against the mole fraction from 0 to 1 for one of the components of a mixture where no complexation occurs, a linear relationship is observed, as shown by the dashed line.

If solutions of two species A and B of equal molar concentration (and hence of a fixed total concentration of the species) are mixed and if a complex form between the two species, the value of the additive property will pass through a maximum (or minimum), as shown by the upper curve.

For a constant total concentration of A and B, the complex is at its greatest concentration at a point where the species A and B are combined in the ratio in which they occur in the complex. The line therefore shows a break or a change in slope at the mole fraction corresponding to the complex. The change in slope occurs at a mole fraction of 0.5 indicating a complex of the 1:1 type.



A plot of an additive property against mole fraction of one of the species in which complexation between the species has occurred. The dashed line is that expected if no complex had formed.

If the magnitude of the measured property, such as absorbance, is proportional only to the concentration of the complex MAn, the molar ratio of ligand A to metal M and the stability constant can be readily determined. The equation for complexation can be written as

$$\mathbf{M + n\ A = MA_n}$$

and the stability constant as $K = \dfrac{[MA_n]}{[M] + [A]^n}$

or, in logarithmic form,

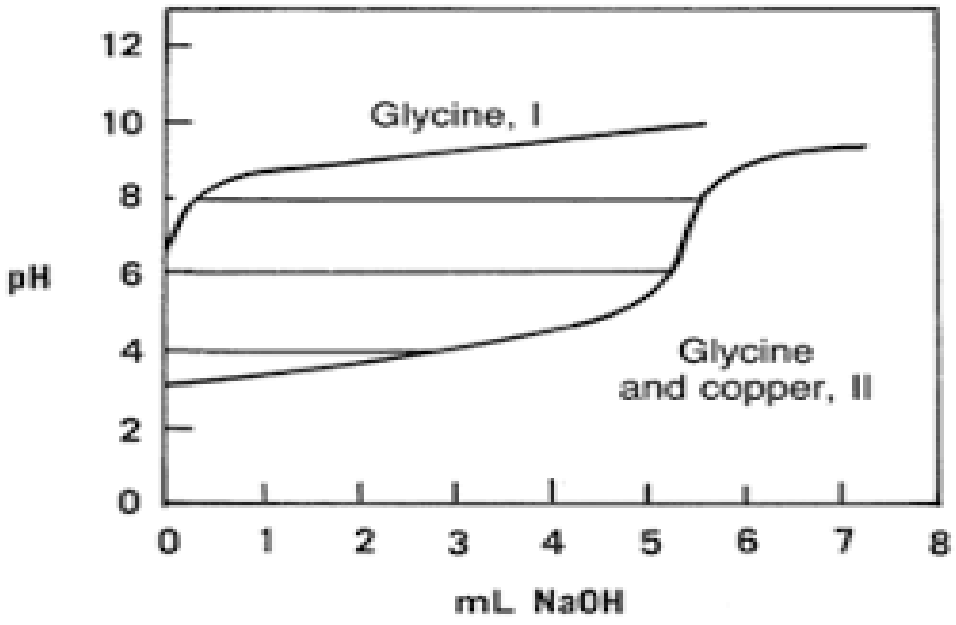
$$\mathbf{\log [M\ A_n] = \log K + \log [M] + n \log [A]}$$

where [MAn] is the concentration of the complex, [M] is the concentration of the uncomplexed metal, [A] is the concentration of the uncomplexed ligand, n is the number of moles of ligand combined with 1 mole of metal ion, and K is the equilibrium or stability constant for the complex. The concentration of a metal ion is held constant while the concentration of ligand is varied, and the corresponding concentration, [MAn], of complex formed is obtained from the spectrophotometric analysis. Now, according to equation, if log [MAn] is plotted against log [A], the slope of the line yields the stoichiometric ratio or the number n of ligand molecules coordinated to the metal ion, and the intercept on the vertical axis allows one to obtain the stability constant, K, because [M] is a known quantity.

pH Titration Method: This is one of the most reliable methods and can be used whenever the complexation is attended by a change in pH. The chelation of the cupric ion by glycine, for example, can be represented as

$$Cu + 2NH_3CH_2COOH \Rightarrow Cu(NH2COO)_2 + 2CH_3COOH$$

Because two protons are formed in the reaction of equation (10-6), the addition of glycine to a solution containing cupric ions should result in a decrease in pH. Titration curves can be obtained by adding a strong base to a solution of glycine and to another solution containing glycine and a copper salt and plotting the pH against the equivalents of base added. The results of such a potentiometric titration are shown in Figure. The curve for the metal–glycine mixture is well below that for the glycine alone, and the decrease in pH shows that complexation is occurring throughout most of the neutralization range. Similar results are obtained with other zwitterions and weak acids (or bases), such as N, N′-diacetylethylenediamine diacetic acid, which has been studied for its complexing action with copper and calcium ions.



Titration of glycine and of glycine in the presence of cupric ions. The difference in pH for a given quantity of base added indicates the occurrence of a complex.

The results can be treated quantitatively in the following manner to obtain stability constants for the complex. The two successive or stepwise equilibria between the copper ion or metal, M, and glycine or the ligand, A, can be written in general as

$$M + A = MA, \qquad \beta = K_1 = \frac{[MA]}{[M][A]}$$

K1 is the equilibrium constant

β is the overall reaction is known as the stability constant.

ñ is the number of ligand molecules bound to a metal ion.

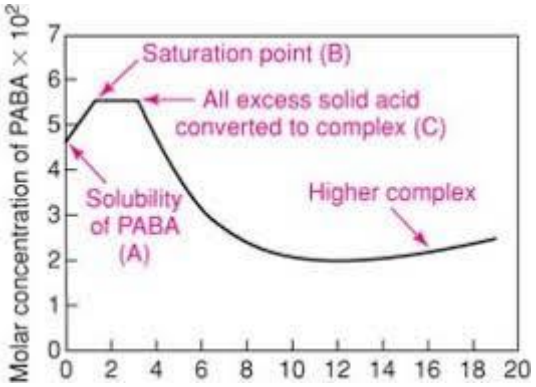
$$n = \frac{\text{total concentration of ligand}}{\text{total concentration metal ion}}$$

Solubility Method: According to the solubility method, excess quantities of the drug are placed in well-stoppered containers, together with a solution of the complexing agent in various concentrations, and the bottles are agitated in a constant temperature bath until equilibrium is attained. Aliquot portions of the supernatant liquid are removed and analysed. used the solubility method to investigate the complexation of p-aminobenzoic acid (PABA) by caffeine. The results are plotted in Figure.

The point A at which the line crosses the vertical axis is the solubility of the drug in water. With the addition of caffeine, the solubility of PABA rises linearly owing to complexation.

At point B the solution is saturated with respect to the complex and to the drug itself. The complex continues to form and to precipitate from the saturated system as more caffeine is added.

At point C all the excess solid PABA has passed into solution and has been converted to the complex. Although the solid drug is exhausted and the solution is no longer saturated, some of the PABA remains uncomplexed in solution, and it combines further with caffeine to form higher complexes such as (PABA-2 caffeine) as shown by the curve at the right of the diagram.



The solubility of para-aminobenzoic acid (PABA) in the presence of caffeine

Subject: Physical Pharmaceutics-I **Unit No: IV**
Faculty: M. MAHESHWAR **Lecture No: 5**
Topic: PROTEIN BINDING **Book Reference: T1, T3**

PROTEIN BINDING

The binding of drugs to proteins contained in the body can influence their action in a number of ways. Proteins may

(a) facilitate the distribution of drugs throughout the body,

(b) inactivate the drug by not enabling a sufficient concentration of free drug to develop at the receptor site, or

(c) retard the excretion of a drug.

The interaction of a drug with proteins may cause

(a) the displacement of body hormones or a co-administered agent,

(b) a configurational change in the protein, the structurally altered form of which is capable of binding a co-administered agent, or

(c) the formation of a drug–protein complex that itself is biologically active.

Among the plasma proteins, albumin is the most important owing to its high concentration relative to the other proteins and also to its ability to bind both acidic and basic drugs. Another plasma protein, α1-acid glycoprotein, has been shown to bind numerous drugs; this protein appears to have greater affinity for basic than for acidic drug molecules.

Protein binding (PB) plays an important role in the pharmacokinetics and pharmacodynamics of a drug. The extent of PB in the plasma or tissue controls the volume of distribution and affects both hepatic and renal clearance.

In many cases, the free drug concentration, rather than the total concentration in plasma, is correlated to the effect. Drug displacement from drug–protein complex can occur by direct competition of two drugs for the same binding site and is important with drugs that are highly

bound (>95%), for which a small displacement of bound drug can greatly increase the free drug concentration in the plasma.

In order to measure free fraction or PB of a drug, ultrafiltration (UF), ultracentrifugation, equilibrium dialysis (ED), chromatography, spectrophotometry, electrophoresis, etc. have been used.

Factors Affecting Protein Binding

The role of hydrophobicity in the formation of water-soluble complexes. The logarithm of the ligand partition coefficient between octanol and water was chosen as a measure of hydrophobicity of the ligand.

Electrostatic forces were not considered as important because all compounds studied were uncharged under the conditions investigated. Donor– acceptor properties expressed in terms of orbital energies (from quantum chemical calculations) and relative donor–acceptor strengths correlated poorly with the formation constants of the complex.

It was suggested that ligand hydrophobicity is the main contribution to the formation of water-soluble complexes. The more hydrophobic chlorobiocin analogues showed the highest percentage of drug bound to human serum albumin. It is suggested that chlorobiocin analogues bind to human albumin at the same site as warfarin. This site consists of two noncoplanar hydrophobic areas and a cationic group.

Warfarin, an anticoagulant, serves as a model drug in Protein Binding studies because it is extensively but weakly bound. Thus, many drugs are able to compete with and displace warfarin from its binding sites. The displacement may result in a sudden increase of the free (unbound) fraction in plasma, leading to toxicity, because only the free fraction of a drug is pharmacologically active.

Subject: Physical Pharmaceutics-I **Unit No: IV**
Faculty: M. MAHESHWAR **Lecture No: 6**
Topic: COMPLEXATION AND DRUG ACTION **Book Reference: T1, T3**

COMPLEXATION AND DRUG ACTION

Many metal complexes have been synthesized and evaluated to overcome the problems of painful insulin injection and side effects for type 1 or type 2 diabetes mellitus. Although, chromium, manganese, molybdenum, copper, cobalt, zinc and vanadium ions have been reported to exhibit insulin-mimetic or enhancing properties in vitro and in vivo, vanadium seems to be the most promising one, especially when coordinated to certain organic ligands.

Encapsulation of the platinum (IV) prodrug met platin in block copolymer nanoparticles increases drug circulation time in the blood and reduces accumulation in the kidneys.

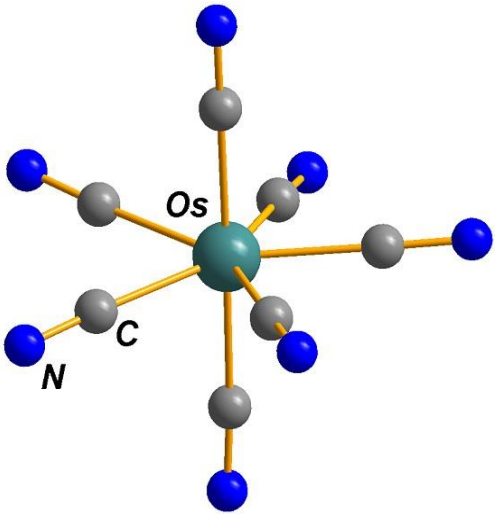
Pyrazinamide (PZA) (pyrazine carboxamide) is a nicotinamide analogue used as a first-line drug to treat tuberculosis. Nicotinic acid (NIC) (pyridine-3-carboxylic acid) known as vitamin B3, niacin, has two important pharmacological properties: peripheral vasodilator and hypocholesterolaemia drug. Its complexes with Cobalt and Copper were synthesized and characterized by elemental analysis.

Guanfacine (GUAF) (N-(diaminomethylidene)-2-(2,6-dichlorophenyl) acetamide), used as antihypertensive drug, is able to form coloured complexes (combination ratio Metal:Ligand 1:2) with Manganese and Cadmium.

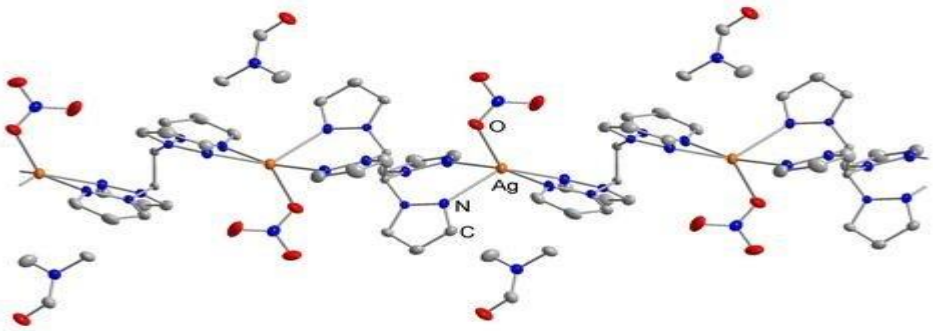
The chemical structure of captopril (CPL), a dipeptide derivative of L-alanine-L-proline with antihypertensive effect, contains bonds such as ─C═O and ─N(─CH2)2 with donor atoms capable of forming Metal-Ligand bonds with the metal ions such as Mn(II), Co(II), Zn(II), Ni(II), and Cd(II) from the N and O atoms of peptide (which act as donors) leads to the formation of stable chelates.

Subject: Physical Pharmaceutics-I **Unit No: IV**
Faculty: M. MAHESHWAR **Lecture No: 7**
Topic: CRYSTALLINE STRUCTURES OF COMPLEXES **Book Reference: T1, T3**

CRYSTALLINE STRUCTURES OF COMPLEXES



HEPTACYANOOSMATE



Subject: Physical Pharmaceutics-I **Unit No: IV**
Faculty: M. MAHESHWAR **Lecture No: 8**
Topic: THERMODYNAMICS OF STABILITY CONSTANTS Book Reference: T1, T3

THERMODYNAMICS OF STABILITY CONSTANTS

The stability constants of metal complexes are related to thermodynamic properties such as free Gibbs energy(ΔG), enthalpy change (ΔH) and entropy change (ΔS). The values can be computed by usual equations:

$$\Delta G = -2.303RT \log K$$

The standard enthalpy change (ΔH) was obtained from the slope of plot of log K vs 1/T

$$\text{Log } K = -\Delta H/2.303RT + \text{constant}$$

When value of K at two temperatures are known. Then K_2 and K_1 are the stability constants at the absolute temperatures T2 and T1respectively.

$$\text{Log } K_2/K_1 = -\Delta H/2.303R\,(T_2-T_1/T_1\,T_2)$$

The standard entropy change is

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

ΔH and ΔS become negative, if stability constants of complexes increase. As binding between donor and acceptor is stronger, then ΔH also become negative. When specificity of interacting site become negative, then ΔS also become negative.

pH BUFFERS AND ISOTONIC SOLUTIONS

Chapter Objectives

At the conclusion of this chapter the student should be able to:

1. Students are able to know the concept of Sorensen's pH scale.
2. Students are able to know & understand the different types of pH determination methods.
3. Students are able to differentiate between different applications of buffers.
4. Understand the main properties of buffer in pharmaceutical and biological systems.
5. Understand the main properties of buffered isotonic solutions.
6. Understand the main properties of isotonicity.
7. Understand the different colligative properties and tonicity.

Subject: Physical Pharmaceutics-I **Unit No: V**
Faculty: M. MAHESHWAR **Lecture No: 1**
Topic: SORENSEN'S pH SCALE **Book Reference: T1, T3**

SORENSEN'S pH SCALE

Electrolyte undergo dissociation in water producing ions. Acids undergo ionization in water giving hydrogen ions or hydronium ions. The thermodynamics definition for pH is defined as negative logarithm of activity of hydrogen ions.

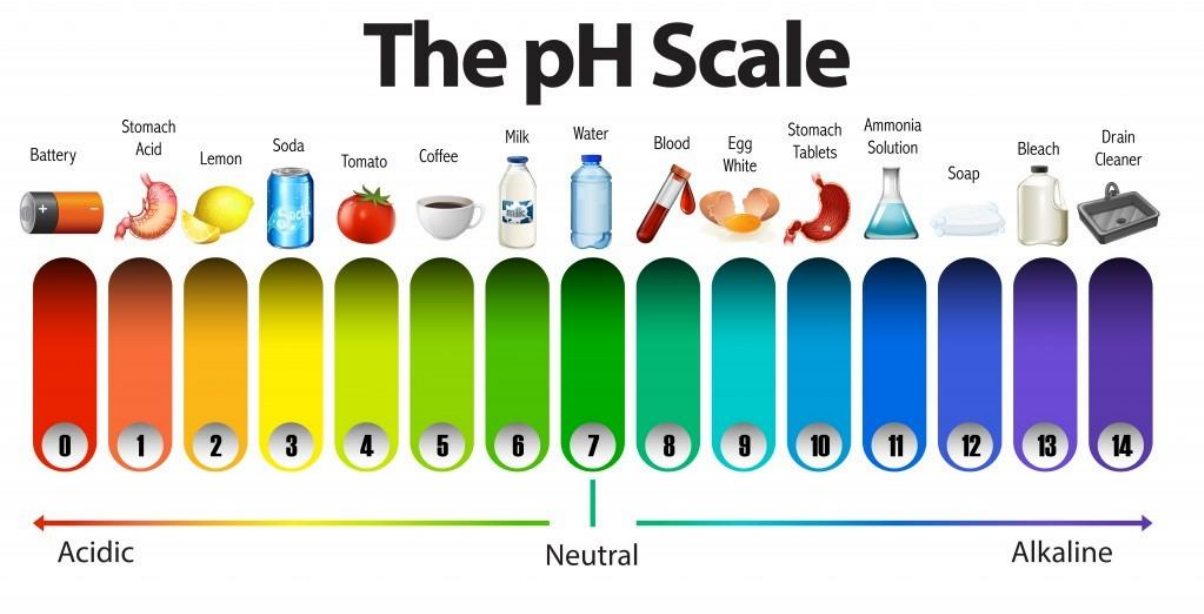
Mathematically pH = -log $[H^+]$ where H^+ is activity of hydrogen ion. pH defined as negative logarithm of hydrogen ion concentration. Sorensen established the term pH, to represent hydrogen ion potential.

The p in pH stands for "potenz" meaning "power" in Danish. Since the scale was given by a Danish Chemist Sorensen. H stands for Hydrogen and is its symbol. Hence H is written in capital letter.

Based on the pH values and different concentration of hydrogen ions, a scale is devised and named after Sorenson, who had developed it. The scale starts with a zero pH, i.e., hydrogen ion concentration is 1(or 100).

It means the solution is strongly acidic. At the other end of the scale, pH is 14 i.e., hydrogen ion concentration is 10-14. It means the solution is strongly alkaline. The central point pH in the scale is 7.0, because [H+] is equal to [OH], i.e., hydrogen ion concentration is 10-7.

pH = 7 means neutral. The region with pH values below 7 is designated as acidic and above pH 7.0 is designated as basic (or alkaline). The pH numbers obtained by measuring solutions containing colloids and non-aqueous solutions have little correlation on the activity scale.



APPLICATION OF pH:

Enhancing solubility

Increasing stability

Improving purity

Optimizing biological activity

Comforting the body

Storage of products

Subject: Physical Pharmaceutics-I **Unit No: V**
Faculty: M. MAHESHWAR **Lecture No: 2**
Topic: pH DETERMINATION **Book Reference: T1, T3**

pH DETERMINATION

Colorimetric Determination of the pH

The basis for what the chemist calls colorimetric analysis is the variation in the intensity of the colour of a solution with changes in concentration (or pH). The colour may be due to an inherent property of the constituent itself (e.g. MnO_4^- is purple) or it may be due to the formation of a coloured compound as the result of the addition of a three suitable reagent (e.g. indicator).

By comparing the intensity of the colour of a solution of unknown concentration (or pH) with the intensities of solutions of known concentrations (or pH), the concentration of an unknown solution may be determined.

Procedure:

1. Estimate the pH of the unknown solution using a universal indicator paper.

2. Select an indicator.

3. Select a buffer system.

4. Prepare a series of solutions with various pH values (10 ml from each, pH steps in the series are 0.2 - 0.2)

5. Add 1 or 2 drops (strictly the same amount) of indicator to each of the solutions and finally to the unknown solution. Compare the colour of the unknown solution to the solutions with known pH.

Electrometric Method

One of the most widely accepted method for the hydrogen ion determination (pH) is the electrometric method. This method is highly accurate and used in laboratory work and by researchers. The accuracy of the pH value is 0.1 to 0.0001.

The standard solutions are used to standardize the pH meter. Here also the temperature is adjusted as mentioned above procedure.

Next, into the water sample, the electrodes are inserted. The beaker is turned and adjusted so that there is good contact between the electrodes and the water.

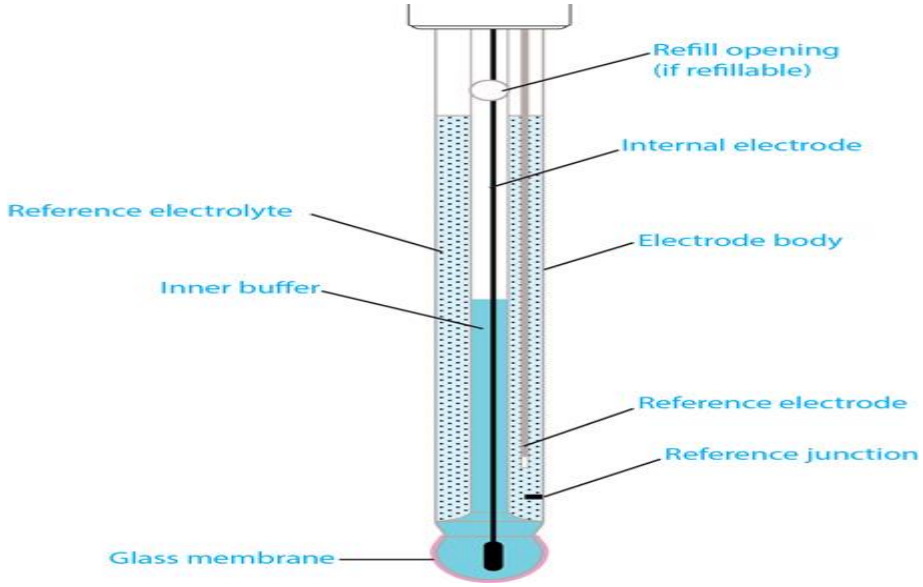
Before starting the reading, the electrodes have to be placed in the solution for more than 30 seconds. This time period is required for the proper stabilizing of the meter to have proper reading. In pH meter that have an automatic reading system, a signal will be provided to tell that the meter is stabilized.

Once the reading is shown, it must be read to the nearest tenth of the whole number. If the value shows to 100^{th} place then it has to be rounded off. The tenth-place digit is left if the 100^{th} place is less than 5. For values greater than 5 after decimal, it is rounded to 1 unit. If the 100^{th} place is equal to 5, the nearest even number is taken as rounded value.

The apparatus must be maintained after each use. The electrodes used are washed thoroughly with distilled water. If there is any form of film around the electrodes, it has to be cleared. Wiping of the electrodes must be avoided as this will result in polarization which will result in slow response of the experiment.

Precautions

1. The pH meter can be standardized by measuring the 7-pH buffer solution or any other solution of standard pH. Sometimes, the manufacturer of the pH meter may suggest other methods of standardizing, which too have to be followed.
2. The electrodes have to be inserted into the water so that it does not touch the bottom of the beaker. Bottom contact may cause damage to the electrodes.
3. Any cause of slow response due to the polarization can be solved by washing the electrodes thoroughly.
4. Periodic check has to be conducted to check the electrodes.



pH ELECTRODE

Subject: Physical Pharmaceutics-I **Unit No: V**
Faculty: M. MAHESHWAR **Lecture No: 3**
Topic: BUFFER EQUATION & BUFFER CAPACITY **Book Reference: T1, T3**

BUFFER EQUATION & BUFFER CAPACITY

Acidic buffer:

It consists of a mixture of weak acid and its salt (strong electrolyte). The ionisation of the weak acid, HA, can be shown by the equation

$$HA \leftrightarrow H^+ + A^-$$

Applying law of mass action,

$$Ka = \frac{[H^+]\,[A^-]}{[HA]}$$

It can be assumed that concentration of A- ions from complete ionisation of the salt BA is too large to be compared with concentration of A- ions from the acid HA.

$$BA \leftrightarrow B+ A$$

Thus, [HA] = Initial concentration of the acid as it is feebly ionised in presence of common ion and [A-] = Initial concentration of the salt as it is completely ionised.

$$So\ [H^+] = Ka\ [Acid]/[Salt]$$

Taking logarithm and reversing sign,

$$-\log [H+] = -\log Ka - \log [Acid]/[Salt]$$

$$or\ pH = \log [Salt]/[Acid] - \log Ka$$

$$or\ pH = pKa + \log [Salt]/[Acid]$$

This is known as Henderson's equation or buffer equation for acidic buffer.

Basic buffer:

It consists of a weak base and its salt with strong acid. Ionization of a weak base, BOH, can be represented by the equation.

$$BOH \leftrightarrow B+ OH$$

Applying law of mass action,

$$Kb = \frac{[B^+][OH^-]}{[BOH]}$$

As the salt is completely ionized, it can be assumed that whole of B+ ion concentration comes from the salt and contribution of weak base to B+ ions can be ignored.

$BA \leftrightarrow B+ + A-$ (Completely ionised)

So $[OH-]= Kb\ [Base]/[Salt]$

or $pOH = \log [Salt]/[Base] - \log Kb$

or $pOH = pKb + \log [Salt]/[Base]$

Knowing pOH, pH can be calculated by the application of the formula. This is known as buffer equation for basic buffer.

The term "buffer capacity" (β) quantifies the change in pH of the solution caused by the addition of a strong acid or base. It is calculated in relation of a buffer solution.

$$\beta = \frac{\Delta n}{\Delta pH}$$

β – buffer capacity,

Δn – amount of added acid/base to the buffer solution [mol],

ΔpH – pH change cause by the addition of acid/base.

The value of the buffer capacity is strongly related to the concentrations of ingredients used and increases with their increase. Buffer solutions with a pH equal to the pKa value of the acid (used to make this solution) have the greatest buffering capacity.

Applications of buffers:

Buffers can help to make drugs safer for consumption by lessening the harsh effects of the chemicals. Most of the medicines are prepared in aqueous solution of different chemicals so these aqueous solutions require a constant pH in order to assure the stability and clinical effectiveness of a medicines and this is done through buffers. Buffers are also added in pharmaceuticals to improve patient comfort and to make longer transportation of medicines

possible. Apart from this buffer are also used to: Maintain some drug or medicine in ionized form as ionized forms are more soluble in aqueous solutions. Maintain some drug or medicine in un-ionized form as un- ionized forms are more soluble in lipids.

Maintain the stability of drugs in different aqueous solutions as many drugs are vulnerable to hydrolysis of aqueous solutions. Maintain the pH of most of the drugs or medicine near to neutral otherwise that specific drug or medicine may cause irritation in body tissues.

Fermentation reactions – such as in beer or yogurt – are highly affected by varying pH. This means it's essential to use buffer solutions to avoid harsh changes and allow fermentation to progress to obtain maximum yield.

During fermentation of baking bread, the pH of the dough will decrease due to released carbon dioxide and other organic acids. In dough, flour and milk act as buffering agents and they resist the pH drop due to the release of carbon dioxide.

Apart from these natural buffers some chemical buffers like calcium carbonate are also used to maintain pH during fermentation process. In bread, the pH of the dough will naturally drop with the production of CO2.

Buffers are also used in foods to maintain the acidity of the food in order to preserve the flavour and appearance of food. Buffers maintain the physical, chemical and microbiological stability of foods.

Specialised buffers are also used extensively in the food industry as food additives. These additives are usually weak acids or their respective salts already naturally present in some foods. Examples: The citrate additives are widely used antioxidants. They are all capable of reducing the chemical reaction that causes the discoloration of fruit, so a member of this group of chemicals is often the additive of choice in fruit products. Potassium citrate is an antioxidant and buffering additive that is found in a number of food products including cakes and biscuits, cheese and jam.

Subject: Physical Pharmaceutics-I **Unit No: V**
Faculty: M. MAHESHWAR **Lecture No: 4**
Topic: BUFFERS IN PHARMACEUTICAL SYSTEMS **Book Reference: T1, T3**

BUFFERS IN PHARMACEUTICAL SYSTEMS AND BIOLOGICAL SYSTEMS

Buffers in pharmaceutical systems particularly in the formulation of ophthalmic solutions. One of the most common biological buffers is phosphate buffered saline (PBS). Phosphate buffered saline contains sodium chloride (NaCl) and dibasic sodium phosphate (Na2PO4). It may also contain potassium chloride (KCl), monobasic potassium phosphate (KH2PO4), calcium chloride (CaCl2), and magnesium sulphate (MgSO4).

The following steps should be helpful in the development of a new buffer.

a- Select a weak acid having a pKa approximately equal to the pH at which the buffer is to be used.

b- from the buffer equation, calculate the ratio of salt and weak acid required to obtain the desired pH. The buffer equation is satisfactory for approximate calculations within the pH range of 4 to 10.

c- Consider the individual concentrations of the buffer salt and acid needed to obtain a suitable buffer capacity. A concentration of 0.05 to 0.5 M is usually sufficient, and a buffer capacity of 0.01 to 0.1 is generally adequate.

d- Other factors of some importance in the choice of a pharmaceutical buffer include availability of chemicals, sterility of the final solution, stability of the drug and buffer on aging, cost of materials, and freedom from toxicity. For example, a borate buffer, because of its toxic effects, certainly cannot be used to stabilize a solution to be administered orally or parenterally.

e- Finally, determine the pH and buffer capacity of the completed buffered solution using a reliable pH meter. In some cases, sufficient accuracy is obtained by the use of pH papers. Particularly when the electrolyte concentration is high, it may be found that the pH calculated by use of the buffer equation is somewhat different from the experimental value. This is to be expected when activity coefficients are not taken into account, and it emphasizes the necessity for carrying out the actual determination.

At a low pH, a base is predominantly in the ionic form, which is usually very soluble in aqueous media. As the pH is raised, more undissociated base is formed, When the amount of base exceeds the limited water solubility of this form, free base precipitates from solution. Therefore, the solution should be buffered at a sufficiently low pH so that the concentration of alkaloidal base in equilibrium with its salt is calculated to be less than the solubility of the free base at the storage temperature.

In Vivo Biologic Buffer Systems

Blood is maintained at a pH of about 7.4. The plasma contains carbonic acid/bicarbonate and acid/alkali sodium salts of phosphoric acid as buffers. Plasma proteins, which behave as acids in blood, can combine with bases and so act as buffers. In the erythrocytes, the two buffer systems consist of haemoglobin/oxyhaemoglobin and acid/alkali potassium salts of phosphoric acid. The dissociation exponent pK1 for the first ionization stage of carbonic acid in the plasma at body temperature and an ionic strength of 0.16 is about 6.1.

Lacrimal fluid, or tears, have been found to have a great degree of buffer capacity, allowing a dilution of 1:15 with neutral distilled water. The pH of tears is about 7.4, with a range of 7 to 8 or slightly higher. It is generally thought that eye drops within a pH range of 4 to 10 will not harm the cornea. However, discomfort and a flow of tears will occur below pH 6.6 and above pH 9.0.

The 24-hr urine collection of a normal adult has a pH averaging about 6.0 units; it may be as low as 4.5 or as high as 7.8. When the pH of the urine is below normal values, hydrogen ions are excreted by the kidneys. Conversely, when the urine is above pH 7.4, hydrogen ions are retained by action of the kidneys in order to return the pH to its normal range of values.

Subject: Physical Pharmaceutics-I **Unit No: V**
Faculty: M. MAHESHWAR **Lecture No: 5**
Topic: BUFFERED ISOTONIC SOLUTIONS **Book Reference: T1, T3**

BUFFERED ISOTONIC SOLUTIONS

Buffered Isotonic Solutions: When two solutions have same osmotic pressure and salt concentration are said to be "isotonic solution". iso (same) and tonic (concentration). Physiologically, isotonic solutions are solutions are solutions having the same osmotic pressure as that of the body fluids when separated by a biological membrane.

Biological fluids including blood and lachrymal fluid normally have an osmotic pressure corresponding to that of 0.9% w/v solution of sodium chloride. Thus 0.9% solution of sodium chloride is said to be isotonic with the physiological fluids. Isotonic solution is a solution having the same osmotic pressure on a body fluid, ophthalmic (eye), nasal (nose), and parenteral (injection) solution should be isotonic.

Solutions containing the same concentration of particles and thus exerting equal osmotic pressure are called iso-osmotic. A 0.9% solution of Nacl (normal saline) is iso-osmotic with blood and tears. The term iso-tonic, meaning equal tone, is sometimes used interchangeably with the term iso-osmotic.

Solution which contain fewer particles and exert a lower osmotic pressure than 0.9% saline are called hypotonic. Administration of a hypotonic solution produces painful swelling of tissues as water passes from the administration site into the tissues or blood cells.

Hypertonic solutions: those solutions exerting higher osmotic pressures are referred to as hypertonic. Hypertonic solutions produce shrinking of tissues as water is pulled from the biological cells in an attempt to dilute the hypertonic solution. Tonicity is a measure of the effective osmotic pressure gradient, as defined by the water potential of two solutions separated by a semipermeable membrane. In other words, tonicity is the relative concentration of solutes dissolved in solution which determine the direction and extent of diffusion.

Subject: Physical Pharmaceutics-I **Unit No: V**
Faculty: M. MAHESHWAR **Lecture No: 6**
Topic: ISOTONICITY **Book Reference: T1, T3**

ISOTONICITY

A solution is isotonic when its effective osmole concentration is the same as that of another solution. In biology, the solutions on either side of a cell membrane are isotonic if the concentration of solutes outside the cell is equal to the concentration of solutes inside the cell.

In this case the cell neither swells nor shrinks because there is no concentration gradient to induce the diffusion of large amounts of water across the cell membrane. Water molecules freely diffuse through the plasma membrane in both directions, and as the rate of water diffusion is the same in each direction, the cell will neither gain nor lose water.

An iso-osmolar solution can be hypotonic if the solute is able to penetrate the cell membrane. For example, an iso-osmolar urea solution is hypotonic to red blood cells, causing their lysis. This is due to urea entering the cell down its concentration gradient, followed by water.

The osmolarity of normal saline, 9 grams NaCl dissolved in water to a total volume of one litre, is a close approximation to the osmolarity of NaCl in blood (about 290 mOsm/L). Thus, normal saline is almost isotonic to blood plasma. Neither sodium nor chloride ions can freely pass through the plasma membrane, unlike urea.

Subject: Physical Pharmaceutics-I **Unit No: V**
Faculty: M. MAHESHWAR **Lecture No: 7**
Topic: COLLIGATIVE PROPERTIES **Book Reference: T1, T3**

COLLIGATIVE PROPERTIES

Colligative properties of solutions depend only on the number of dissolved particles (molecules or ions, small or large) in solution and not on their identity.

I. Osmotic pressure

II. Vapor pressure lowering

III. Boiling point elevation

IV. Freezing point depression

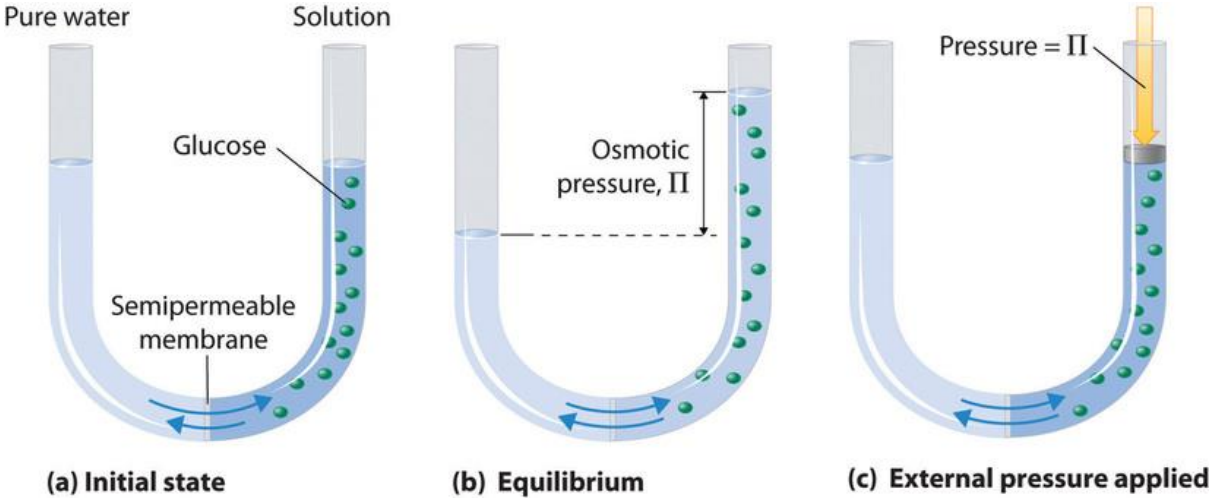
Colligative Properties of Electrolytes depend on the number of particles dissolved, solutions of electrolytes (which dissociate in solution) show greater changes than those of nonelectrolytes. e.g. NaCl dissociates to form two ion particles; It lowers freezing points almost twice as much as methanol, a nonelectrolyte $CaCl_2$ dissociates to form three ion particles; It lowers freezing points almost three times as much as methanol.

I. Osmotic pressure

Osmosis is the process in which a liquid pass through a membrane whose pores permit the passage of solvent molecules but are too small for the larger solute molecules to pass through.

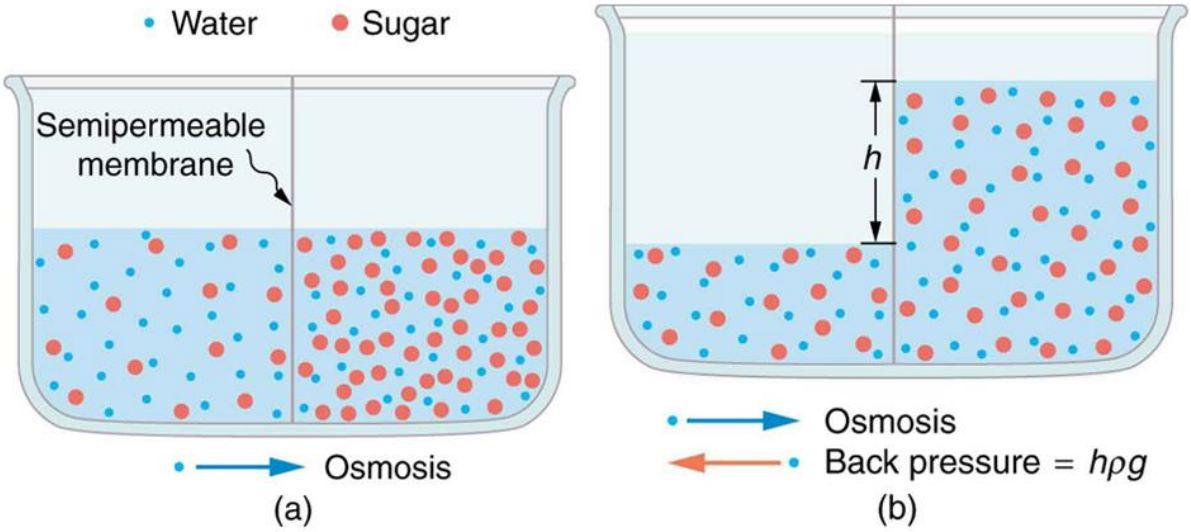
Semipermeable Membranes and Osmotic flow

The osmotic cell has compartments contain water, but the one on the right also contains a solute whose molecules (represented by green circles) are too large to pass through the membrane. Many artificial and natural substances are capable of acting as semi-permeable membranes. The walls of most plant and animal cells fall into this category.



If the cell is set up so that the liquid level is initially the same in both compartments, you will soon notice that the liquid rises in the left compartment and falls in the right side, indicating that water molecules from the right compartment are migrating through the semipermeable membrane and into the left compartment. This migration of the solvent is known as osmotic flow, or simply osmosis.

Osmotic flow is simply diffusion of a solvent through a membrane impermeable to solute molecules. Now take two solutions of differing solvent concentration, and separate them by a semipermeable membrane. Being semipermeable, the membrane is essentially invisible to the solvent molecules, so they diffuse from the high concentration region to the low concentration region just as before. This flow of solvent constitutes osmotic flow, or osmosis.

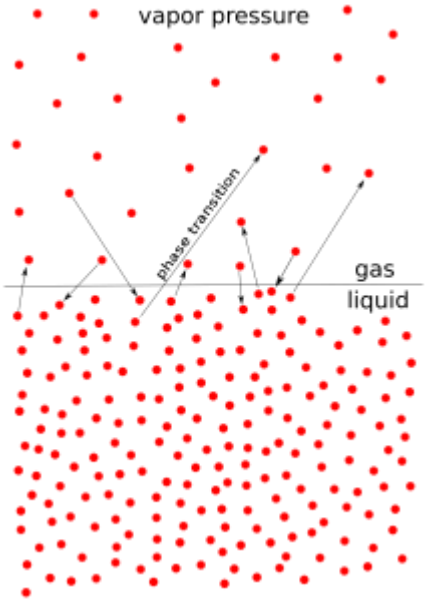


Water molecules (blue) passing freely in both directions through the semipermeable membrane, while the larger solute molecules remain trapped in the left compartment, diluting

the water and reducing its escaping tendency from this cell, compared to the water in the right side. This results in a net osmotic flow of water from the right side which continues until the increased hydrostatic pressure on the left side raises the escaping tendency of the diluted water to that of the pure water at 1 atm, at which point osmotic equilibrium is achieved.

II. Vapor pressure lowering

Vapour pressure is the pressure exerted by the vapours over the liquid under the equilibrium conditions at a given temperature. Now let us take an example of a pure liquid, the surface of the liquid is occupied by the molecules of the liquid. Suppose a non-volatile solute is now added to this pure liquid. Since the solute molecules are non-volatile, the vapour above the solution consists of only solvent (pure liquid) molecules. After adding the solute, the vapour pressure of the solution is found to be lower than that of the pure liquid at a given temperature.



This lowering in vapour pressure is due to the fact that after the solute was added to the pure liquid (solvent), the liquid surface now had molecules of both, the pure liquid and the solute. The number of solvent molecules escaping into vapour phase gets reduced and as a result the pressure exerted by the vapour phase is also reduced. This is known as relative lowering of vapour pressure. This decrease in vapour pressure depends on the amount of non-volatile solute added in the solution irrespective of its nature and hence it is one of the colligative properties.

Let us assume a binary solution in which the mole fraction of the solvent be x_1 and that of the solute be x_2, p1 be the vapour pressure of the solvent and p_1^o be the vapour pressure of the solvent in pure state.

According to Raoults Law:

$$p_1 = x_1 p_1^o$$

The decrease in vapour pressure of the solvent (Δp_1) is given by:

$$\Rightarrow \Delta p_1 = p_1^o - p_1$$

$$\Rightarrow \Delta p_1 = p_1^o - p_1^o x_1$$

$$\Rightarrow \Delta p_1 = p_1^o (1 - x_1)$$

Since we have assumed the solution to be binary solution, $x_2 = 1 - x_1$

$$\Rightarrow \Delta p_1 = p_1^o x_2$$

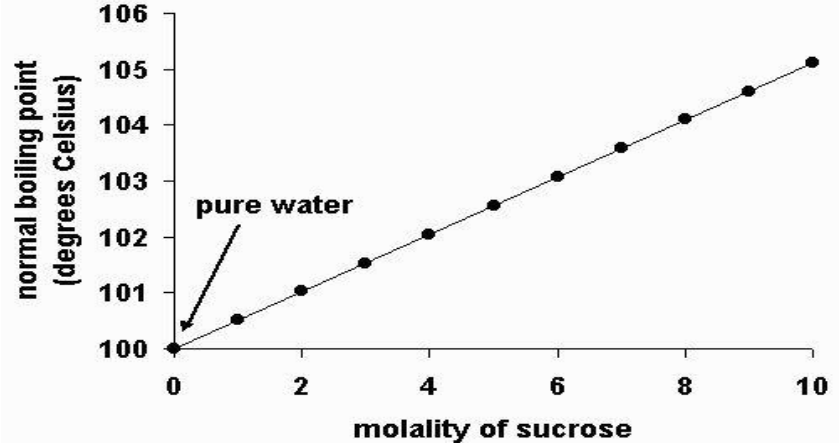
$$\Rightarrow x_2 = \Delta p_1 / p_1^o$$

The above equation gives the relative lowering in vapour pressure which is equal to the mole fraction of the solute.

III. Boiling point elevation

Boiling point elevation refers to the increase in the boiling point of a solvent upon the addition of a solute. When a non-volatile solute is added to a solvent, the resulting solution has a higher boiling point than that of the pure solvent. For example, the boiling point of a solution of sodium chloride (salt) and water is greater than that of pure water.

Boiling point elevation is a colligative property of matter, i.e. it is dependent on the solute-to-solvent ratio but not on the solute's identity. This implies that the elevation in the boiling point of a solution depends on the amount of solute added to it. The greater the concentration of solute in the solution, the greater the boiling point elevation.

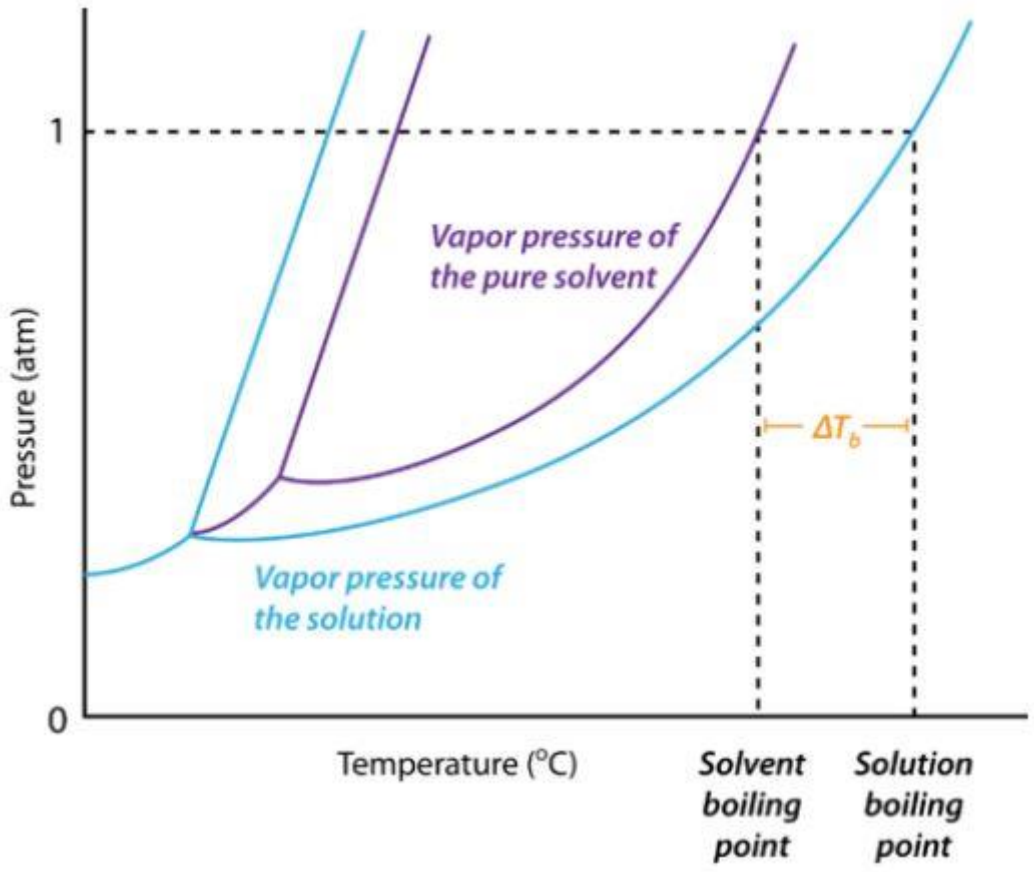


A graph detailing the elevation in the boiling point of water upon the addition of sucrose is provided above. At 1atm of pressure, pure water boils at 100°C. However, a 10 molal solution of sucrose in water boils at approximately 105°C.

The boiling point of a liquid is the temperature at which its vapour pressure is equal to the pressure of its surrounding environment. Non-volatile substances do not readily undergo evaporation and have very low vapour pressures (assumed to be zero). When a non-volatile solute is added to a solvent, the vapour pressure of the resulting solution is lower than that of the pure solvent.

Therefore, a greater amount of heat must be supplied to the solution for it to boil. This increase in the boiling point of the solution is the boiling point elevation. An increase in the concentration of added solute is accompanied by a further decrease in the vapour pressure of the solution and further elevation in the boiling point of the solution.

A pressure v/s temperature graph detailing the boiling point elevation of a solution is provided below.



Here, ΔT_b represents the elevation in the boiling point of the solution. From the graph, it can be observed that –

1. The freezing point of the solution is lower than that of the pure solvent (freezing point depression).
2. The boiling point of the solution is higher than that of the pure solvent.

Note: The boiling point of a liquid is also dependent on the pressure of its surroundings (which is why water boils at temperatures lower than 100°C at high altitudes, where the surrounding pressure is low). The boiling point of a solution containing a non-volatile solute can be expressed as follows:

Boiling point of solution = boiling point of pure solvent + boiling point elevation (ΔT_b)

The elevation in boiling point (ΔT_b) is proportional to the concentration of the solute in the solution. It can be calculated via the following equation.

$$\mathbf{\Delta T_b = I K_b m}$$

Where,

- i is the Van't Hoff factor
- K_b is the ebullioscopy constant
- m is the molality of the solute

The ebullioscopy constant (K_b) is often expressed in terms of ^oC/molal or $^oC.kg.mol^{-1}$. The degree of dissociation of the solute and the molar mass of the solute can be calculated with the help of the boiling point elevation formula.

IV. Freezing point depression

Freezing point depression is a colligative property observed in solutions that results from the introduction of solute molecules to a solvent. The freezing points of solutions are all lower than that of the pure solvent and is directly proportional to the molality of the solute.

$$\mathbf{\Delta T_f = T_f\,(solvent) - T_f\,(solution) = K\ f\ m}$$

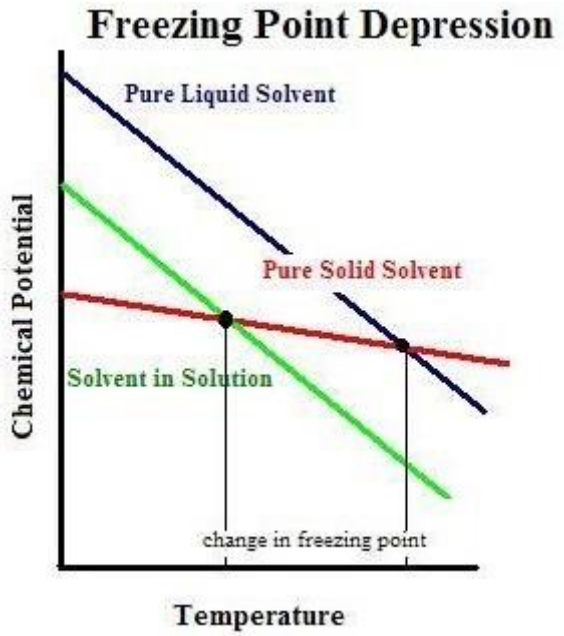
where ΔT_f is the freezing point depression, T_f (solution) is the freezing point of the solution, T_f (solvent) is the freezing point of the solvent, K_f is the freezing point depression constant, and m is the molality.

The freezing point and boiling point of a pure solvent can be changed when added to a solution. When this occurs, the freezing point of the pure solvent may become lower, and the boiling point may become higher. The extent to which these changes occur can be found using the formulas:

$$\Delta T_f = K_b\, m \quad \text{or} \quad \Delta T_f = K_f\, m$$

where m is the solute molality and K values are proportionality constants; (K_f and K_b for freezing and boiling, respectively.

Freezing point is reached when the chemical potential of the pure liquid solvent reaches that of the pure solid solvent. Again, since we are dealing with mixtures with decreased chemical potential, we expect the freezing point to change. Unlike the boiling point, the chemical potential of the impure solvent requires a colder temperature for it to reach the chemical potential of the pure solid solvent. Therefore, a **freezing point depression** is observed.



ISOTONICITY ADJUSTING METHODS

Solutions that have the same osmotic pressure as that of body fluids are said to be isotonic with the body fluid. Body fluids such as blood and tears have osmotic pressure corresponding to that of 0.9% Nacl or dextrose aqueous solution; thus, a 0.9% Nacl or 5 %, dextrose solution is called as isosmotic or isotonic. The term isotonic means equal tone, and is used interchangeably with isosmotic with reference to specific body fluids. For example, a 0.9% w/v solution of Nacl in water is considered to be isotonic in relation to RBC's and their semi-permeable membranes.

Requirements of isotonic solutions are that they must not cause any contraction or swelling of the tissues.

The product must not produce discomfort when installed in the eye, nasal tract, blood, or other body tissue. On addition of 0.9gm Nacl/100ml (0.9%) in to blood (defibrinated), the cells retain their normal size. Isotonic solution should be restricted to solutions having equal osmotic pressure with respect to a particular membrane. The addition of any compound to a solution affects its isotonicity, causing changes in osmotic pressure of a solution. It should not be affected only by drugs but also by any buffer components added in the formulation. Therefore, it is necessary to add additional Nacl to bring the solution to isotonicity. Adjustment of isotonicity is required for several dosage forms such as parenteral solutions, e.g., IV infusions, irritating solutions, lotions for open wounds, subcutaneous injections, preparations meant for diagnostic applications, solutions meant for intrathecal injections, nasal drops and ophthalmic drops.

Isotonicity can be calculated from the colligative properties of drug solutions. If solutions are injected or introduced in to eyes and nose, these are to be made isotonic in order to avoid haemolysis of RBC's and to avoid pain and discomfort. This is possible for either manufactured or extemporaneous prepared solutions. By using the appropriate calculations based on colligative properties of solutions, it is easy to determine the amount of adjusting agents to be added. It helps to overcome the side effects caused from administering solutions which contain adjusting agents less or more than isotonic solutions.

The three frequently used methods to calculate isotonicity of the solutions are described below. Class-1 Methods: Nacl or some other substances is added to the solution of the drug to lower the freezing point of the solution to -0.52^{o}C and thus make the solution isotonic. Examples of this class- 1) Cryoscopic method 2) Sodium chloride equivalent method.

Class-2 Methods: Water is added to the drug in a sufficient amount to make it isotonic. Then the preparation is brought to its final volume with an isotonic or buffered isotonic solution. Examples of this class- White Vincent method.

Class-3 Methods: Freezing point depression and L iso values for number of drugs are estimated theoretically from the molecular weight of the drug and can be used to calculate the amount of adjusting substance to be added in order to make the solution isotonic.

Cryoscopic method: In this method, the quantity of each substance required for an isotonic solution can be calculated from the freezing point depression values. A solution which is isotonic with blood has a ΔT_f of 0.52°C. Therefore, the freezing point of drug solution 'x' must be adjusted to this valve. In case of drug solutions, if it is not possible to adjust tonicity by altering the drug concentration, then an adjusting substance is added to achieve desired tonicity. The weight (in grams) of adjusting substance can be calculated in manner described below. For example, the drug concentration in 100ml solution is a gram, then If sodium chloride is used as adjusting substance whose of solution is 0.58°C (0.576°C) then

$$\mathbf{W = 0.52- x / 0.58}$$

Sodium chloride equivalent method: Tonicity equivalent or sodium chloride equivalent method is used to adjust the tonicity of pharmaceutical solutions. Sodium chloride equivalent (E) of a drug is the amount of sodium chloride that is equivalent to 1 gm of the drug. The percent of sodium chloride required for adjusting the isotonicity can be calculated using the following equation.

$$\mathbf{PSA = 0.9 – (PSM \times E \text{ of medicament})}$$

Where, PSM = Percent strength of medicament

PSA = Percent of sodium chloride for adjustment of isotonicity

White-Vincent method: This method involves the addition of water to the given amount of drug to make isotonic solution, followed by the addition of some other isotonic solution (e.g. 0.9% NaCI) to make the final volume. The volume of water that should be added in given amount of drug to make isotonic solution is calculated by using following formula;

$$\mathbf{V = W \times E \times 111.1}$$

Where, V = volume of water needed to make isotonic solution

W = given weight of drug in grams

E = NaCI equivalent value of drug

111.1 = constant

The L ISO – Method: The E Nacl value of tonicity adjusting substances can also be calculated from the substances. The L iso values of the tonicity adjusting substances are given in table and are mentioned as constants in many references. In this method, the freezing point

depression equation is used to calculate the amount of the isotonicity. Above equation is used to calculate the amount of adjusting substance (sodium chloride) required for making the solution isotonic. It is valid for 100 ml solution and adjusting substance that must be added to hypotonic solution of drug to bring to tonicity. As the freezing point depression for solutions of electrolytes are than those calculated by the equation as

$$\mathbf{\Delta T_f = L\ iso\ C}$$

Where = L iso is the molal freezing point depression of water considering the ionization of electrolyte. i.e., and C is the concentration of the solution in molarity.