ejpmr, 2016,3(4), 540-548

SJIF Impact Factor 3.628

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 3294-3211

EJPMR

ENHANCEMENT OF WATER SOLUBILITY OF POORLY WATER SOLUBLE DRUGS: A REVIEW

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Article Received on 20/02/2016 **Article Revised on 11/03/2016** **Article Accepted on 31/03/2016**

1. INTRODUCTION

The solubility of a substance (solute) is the maximum quantity of solute that can dissolve in a certain quantity of solvent at a specified temperature and pressure. In the other words the solubility can be define as the ability of one substance to form a solution with another substance in which one is solute and another is solvent. The substance to be dissolved is called as solute and the dissolving fluid in which the solute dissolve is called as solvent, which together form a solution.[1] Solubility, dissolution of solute in solvent to give a homogenous system, is important parameters to achieve desired concentration of drug in systemic circulation for pharmacological response. Today Poorly soluble drugs are problem in pharmaceutical formulations, poor solubility, making them poor candidates as new drugs. And about 40% drugs from newly developed chemical entities are lipophilic in nature and fail to reach market due to poor water solubility. The poor solubility of drugs remains one of the most challenging aspects in formulation development. We can overcome from this problem by combinatorial chemistry and various methods to improve the dissolution of poorly soluble drugs. It needs to improve the solubility and dissolution rate for poorly soluble drugs because these drugs possess low absorption and bioavailability.[2] Any drug to be absorbed must be present in an aqueous solution at the site of absorption. The oral route of administration is the most preferred and widely acceptable due to ease of ingestion for many drugs. Drugs with slow dissolution rate show the incomplete absorption leading to low bioavailability by oral administration. Various techniques are used for the improvement of the solubility of poorly water soluble drugs.

Definition of different terms of solubility explained by Indian Pharmacopoeia 1996 shown in table.1

Definition	Parts of solvents required for one part of solute (in ml)
Very soluble	<1
Freely soluble	1-10
soluble	10-30
Sparingly soluble	30 – 100
Slightly soluble	100 – 1000
Very slightly soluble	1000 - 10,000
Insoluble	> 10,000

2. FACTOR INFLUENCING SOLUBILITY

Solute related factor

- Nature of solute- Size, Shape and surface area
- Physicochemical properties- melting point, heat of fusion, molar volume and pKa
- Physical forms- Salt, crystalline state, Nature of the solid, and polymorphism.

Solvent related factor

- Nature of the solvent, i.e., Polarity, pH of the medium, volume of solvent employed.

-**Environment related factor:** Temperature and pressure.

- Formulation related factor: Other ingredients.

1. Important Factors Influencing Solubility

Particle size -The solubility of drug is often essentially related to drug particle size; as a particle become smaller, the surface area to volume ratio increases. The larger surface area permits greater interaction with the solvent which causes an increase in solubility.

Temperature -If the solution process absorbs energy then the solubility increases with rise in temperature. If

the solution process release energy then the solubility will decrease with increasing temperature.

Pressure -For gaseous solute, an increase in pressure increase solubility and a decrease in pressure decrease the solubility for solid and liquid,a change in pressure practically has no effect on solubility.

Nature of the solid -Depanding upon the internal structure of the solid it may be either crystalline amorphous .Crystalline structure exhibit low solubility while amorphous forms exhibit low solubility while amorphous forms exhibit high solubility.

Polymorphism -The order for dissolution of different solid forms of a drug is Amorphous > Meta stable polymorph > Stable Polymorph.

Stearic affect -Solubility is also affected by dimension of structure and its configurations.

Solvent-Solubility is greatest between materials with similar polarities and this is defined by hydrogenbonding.

- **Weak hydrogen bond liquid** Hydrocarbons, chlorinated hydrocarbons, and nitro- hydrocarbons.
- **Moderate Hydrogen bond liquid** Ketones, esters, ethers, and glycol mono-ethers.
- **Strong Hydrogen bond liquid** Alcohols, amines, acids, amides and aldehydes.

pH -pH of a substance is related to its pKa and concentration of ionised and un-ionised forms of thesubstance by the equation: pH = pKa + log [A-/HA]
where pKa = Dissociation constant.

If the substance is brought outside its pKa (pH value where half of the substance is ionised and half un-ionised), then solubility will be changed because of introduction of new intermolecular forces, mainly ionic attraction forces.

Dielectric Constant -The solubility is a function of dielectric constant of polar and nonpolar medium. Most often, withhydrophobic drugs, the solubility decreases with increasing dielectric constant.

2. General principles related solubility
- Amorphous forms of drugs have greater aqueous solubility than the crystalline forms
- Among crystals, metastable forms of drugs have greater aqueous solubility than the stable forms.
- Anhydrous forms of drugs have greater aqueous solubility than hydrates forms.
- Organic solvates of drugs have greater aqueous solubility than unsolvated forms.
- salt forms of drugs have greater aqueous solubility than non-salt forms, provided common ion effect is not influenced.[6]

3. MECHANISM OF SOLUBILITY
The 'solubility' is define as maximum amount of a solute that can be dissolved in a given amount of solvent. It may be quantitatively and qualitatively. Quantitatively, it may defined as concentration of solute in a saturated solution at a particular temperature. In qualitative terms, it may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. The solubility of a substances can be expressed through various concentration expression as parts, percentage, molarity, molality, volume fraction, mole fraction etc. In solubility, both repulsive and attractive forces which are involved. The intermolecular forces and valence bond are as follows which involve in solubility

1. Intermolecular force
· Dipole-dipole interaction (Keesome interactions)
· Dipole- induced dipole interaction(Debye interactions)
·Induced-dipole interaction-Induced-dipole interaction (London dispersion forces)
· Ion-dipole interaction
· Hydrogen bonds

2. Valence Bonds
. Heteropolar Bond
· Electrovalent Bond
· Covalent Bond
· Homo-polar Bond

Intermolecular force
1. Dipole-dipole interaction
Dipole dipole interactions involves electrostatic interaction between permanent dipole in molecules. These interaction ten to align the molecules to increase attraction (reducing potential energy)**(fig:1)**. An example of BrCl **(fig:2)**: the positive end of a polar molecular will attract the negative end of a polar molecule will attract the negative end of the another molecule and influence interaction between two different molecules .Polar molecules have a net attraction between those two molecules.

These molecules contain dipolar groups, but have no overall dipole moment. This occurs when there is symmetry within the molecule that causes the dipole to cancel each other e.g. tetrachloromethane.

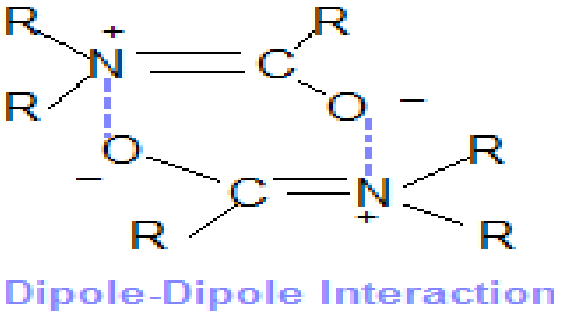

Fig: 1 Dipole – Dipole Interaction

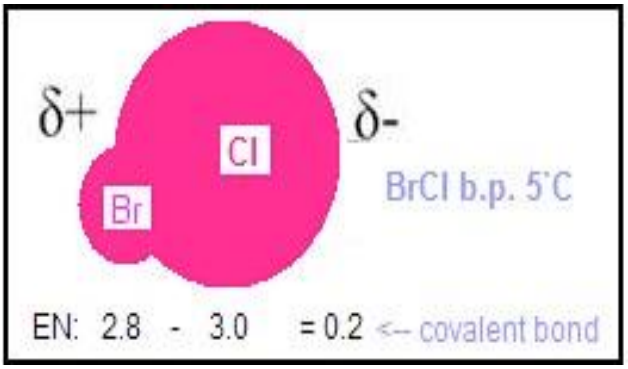

Fig: 2Dipole – Dipole Interaction in BrCl

2. Dipole- induced dipole interaction (Debye interactions)- The induced dipole forces appears from the induction (known polarization), it is the attraction interaction between a permanent multipole on one molecule with an induced multipole on another. It is called the Debye force, named after Peter J. W. Debye.

This type of interaction can be expected between any polar molecule and non-polar / symmetrical molecule. But the dipole-induced dipole interaction is far weaker than dipole-dipole interaction, & stronger than the London Dispersion Force.

3. Induced-dipole interaction-(London dispersion forces) – The London dispersion force involves correlated movement of the electrons in interacting Molecules Electrons that belong to different molecules start "fleeing" and avoiding each other at the short intermolecular distances, which is frequently form of instantaneous dipole that attract each other **(fig:3)**.[7]

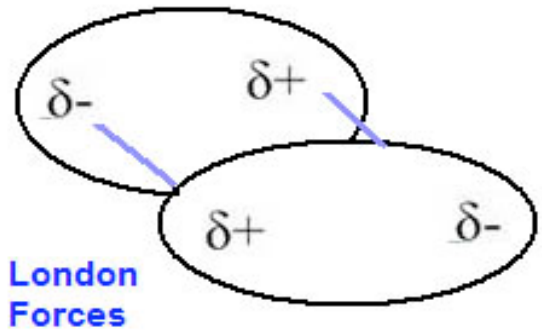

Fig:3 Induced – Dipole Interaction-(London dispersion forces)

4. Ion dipole interaction – This force is similar to dipole-dipole interactions but only diffrent in it involve ion and this Ion-dipole force are stronger than dipole-dipole interaction because the charge of any ion is much greater than the charge of a dipole moment. Ion-dipole force stronger than hydrogen bonding.

Example - Anion-dipole force consists of ion and a polar molecule interacting to this ion molecule. They align so that the positive and negative groups are next to one another, it allowes for maximum attraction between ion and polar group **(fig:4)**.

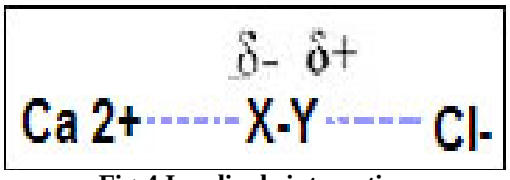

Fig:4 Ion dipole interaction

5. Hydrogen bonding – Hydrogen bond is the attraction between the ion pair of an electronegative atom and a hydrogen atom that is bonded to either nitrogen, oxygen or fluorine **(fig:5&6)**. It is often described as a strong electrostatic dipole- dipole interaction. Intermolecular hydrogen bonding is responsible for the high boiling point of water (100°) compared to the others compounds, which have no hydrogen bonds. This intermolecular hydrogen bonding is partly responsible for the secondary, tertiary ,and quaternary structures of protein and nucleic acids. It having an important role in the structure of polymer, (both synthetic and natural).[7]

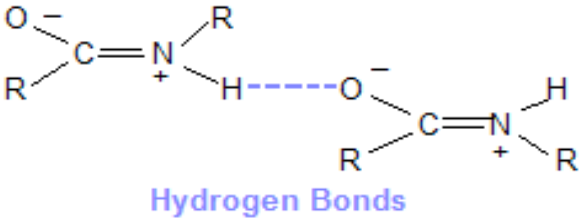

Fig:5 Hydrogen Bonding

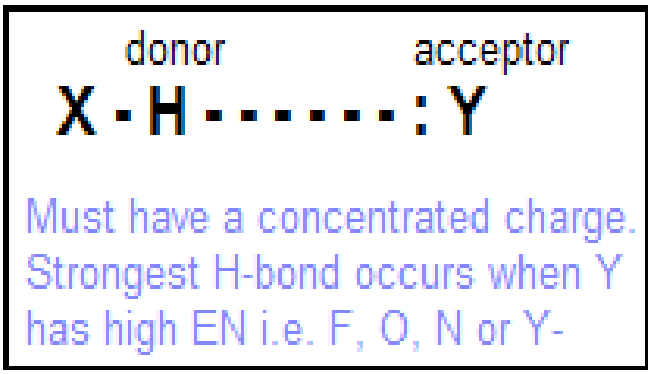

Fig:6 Hydrogen Bonding between H and F, O, N.

Valence Bonds

1. Heteropolar and Homopolar Bonding - The heteropolar bond of a molecule, for example the salt molecule NaCl. When the Na atom comes closer to the Cl atom, an electron transferred from Na to Cl which results in a reduction of the total energy, and the ions are held together by an electrostatic bond. The electron transfer and potential difference of the cations with respect to the neutral atoms can only be explained with quantum mechanics. In homopolar bonding, there is no

transfer of charge. The simplest example is thehydrogen molecule H_2.

2. Electrovalent bond – The chemical bond formed by transfer of electron from a metal to a non- metal is known as ionic or electrovalent bond. For example, when sodium metal and chlorine gas are brought into contact, they react violently and we obtain sodium chloride**(fig:7)**. This reaction is shown below

$2Na(s) + Cl2(g) \longrightarrow 2NaCl(s)$

Note that the sodium cation has 11 protons but 10 electrons only. It has 8 electrons in the outermost (L) shell. Thus, sodium atom has attained the noble gas configuration by losing an electron present in its outermost shell. Loss of electron results into formation of an ion and this process is called *ionization*. Thus, according to octet rule (the atoms have a tendency to acquire stable state or noble gas configuration. Therefore, they combine with atoms of other elements to acquire 08 electrons in the valence shell by giving, taking or sharing of electrons. the atoms have a tendency to acquire stable state or noble gas configuration. The ionization of sodium atom to give sodium ion requires an energy of 496 kJ mol–1. This is the basic cause of Chemical bonding and is called **Octet Rule.**) sodium atom can acquire stability by changing to sodium ion (Na+).

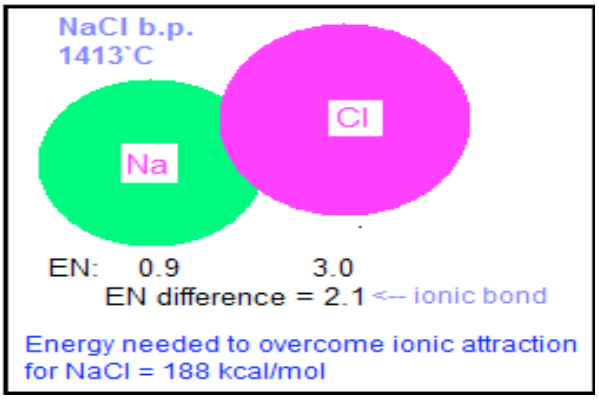

Fig: 7Electrovalent Bond in NaCl

Now, chlorine atom having the atomic number 17, has the electronic configuration 2,8,7. It completes its octet by gaining one electron from sodium atom with electronic configuration 2, 8, 1.

Both sodium ion (Na+) and chloride ion (Cl–) combine together by ionic bond and become solid sodium chloride (NaCl).In the above process, the chlorine atom has gained an additional electron hence it has become a negatively charged ion (Cl–). Such, a negatively charged ion is called an **anion**. Chloride ion has 8 electrons in its outermost shell and it therefore, has a stable electronic configuration according to the octet rule. The formation of chloride ion from the chlorine atom releases 349 kJ mol-1 of energy. Since the **cation**(Na+) and the **anion** (Cl–) formed above are electrically charged species, they are held together by Coulombic force or electrostatic force of attraction. This **electrostatic force of attraction which holds the cation and anion togetheris known as electrovalent bond or ionic bond**.

3. Covalent Bond – When the two hydrogen atoms come closer, there is an attraction between the electrons of one atom and the proton of another and there are repulsions between the electrons as well as the protons of the two hydrogen atoms. In the beginning, when the two hydrogen atoms approach each other, the potential energy of the system decreases due to the force of attraction. The value of potential energy reaches a minimum at some particular distance between the two atoms. If the distance between the two atoms further decreases, the potential energy increases because of the forces of repulsion.

The covalent bondforms when the forces of attraction and repulsion balance each other and thepotential energy is minimum.

It is this lowering of energy which leads to the formation of the covalent bond. Formation of covalent bond in H2 can be shown as

$H. + .H \longrightarrow H : H \longrightarrow H2$

The two hydrogen atoms are said to be bonded together byone covalent bonds. Such a bond consisting of two covalent bonds is also known as a **single bond.**
H-H

An oxygen molecule can be represented as follows
O= O

The two oxygen atoms are said to be bonded together by two covalent bonds. Such a bond consisting of two covalent bonds is also known as a **double bond.**

These three bonds are represented by drawing three lines between the two nitrogen atoms can be represented as follows
N=N

The two nitrogen atoms are said to be bonded together by three covalent bonds. Such a bond consisting of three covalent bonds is also known as a **triple bond.**[8]

4. IMPORTANCE OF SOLUBILITY ENHANCEMENT

- To achieve preferred concentration of drug in Systemic circulation for achieving required pharmacological response, solubility is an important parameter.

- Drugs which are poorly soluble frequently require high doses and also need high dosage regimens for

increase in therapeutic plasma concentrations after oral administration.

- With preparation and development of new chemical entities low drug solubility is the main problem.
- One of the important rate limiting step for orally administered drug is drug solubility for its desired concentration for achieving desired pharmacological response.
- Water is the solvent of excellent for liquid pharmaceutical formulations.
- Most of the drugs like weakly acidic or weakly basic having poor aqueous solubility.
- Slow drug absorption leads to insufficient and gastrointestinal mucosal toxicity and variable bioavilability due to poor water solubility of drug.[8]
- For orally administered drug solubility is most important factore because one rate limiting parameter to achieve their desired oral bioavailability and permeability. The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability.
- Solubility is important factor for other dosage forms like parenteral formulation as well. The compounds with low solubility of compound shows negative effects include poor absorption and bioavailability, insufficient solubility for iv dosing, development challenges which leads to increasing the development cost and time, burden shifted to patient (frequent high–dose administration.

5. TECHNIQUES FOR SOLUBILITY ENHANCEMENT

(1) Size reduction

The solubility of a drug is related to the particle size. Particle size can reduced by sonosuspension, micronisation and nanosuspension supercritical fluid process. In each technique different equipments are used for reduction of the particle size.[11] Reduction of particle size of a drug by jet mill, rotor stator colloidal mill, ball mill, etc. leads to increase in surface area which enhanced dissolution of drug. But also there are limitation this process includes thermal and physical stress on drug product that leads to degradation or instability and limited opportunity to control several characteristics of final product like shape, size, morphology, surface properties, and electrostatic charges. Example of particle size reduced preparations are – Nanosuspension (applied to tarazepide, atovaquone, amphotericin B, etc.), Micronization (applied to griseofulvin, progesterone, spironolactone diosmin, and fenofibrate, etc)

- **Nanosuspension technology:** Nanosuspension technology has been used for developed effective delivery of poor water-soluble drug. Nanosuspension is sub-micron colloidal dispersion of pure particles of drugs, which is stabilized by the help surfactants for either topical or oral or parentral or pulmonary route. Particle size is usually less than one micron ranging between 200 and 600 nm in nonosuspention.

-Micronization: The solubility of drug is related to its particle size. By reducing the particle size, the surface area increased which improves the dissolution properties of the drug. Conventional methods of particle size reduction are, ha disadvantage which leads to drug instability. The micronisation is a technique used to increased surface area for dissolution. It increases the dissolution rate of drugs by increasing surface area; it does not increase equilibrium solubility. Micronization of drugs is done by milling techniques by using rotor stator, colloid, jet mills etc.

-Sonocrystallisation: Recrystallization of poorly soluble materials by using antisolvents and liquid solvents has also been used successfully to reduce particle size. It is a novel approach for particle size reduction on the basis of crystallisation by using ultrasound. Sonocrystallisation utilizes ultrasound power in frequency range of 20–100 kHz for inducing crystallisation. It's enhances the nucleation rate and also enhances an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients.

- **Supercritical fluid process:** A SCF are exists as a single phase above its critical temperature (Tc) and pressure (Pc), they are intermediate between those of pure liquid and gas (i.e., liquid-like density, gas-like compressibility and viscosity and higher diffusivity than liquids). Moreover, the density, transport properties (such as viscosity and diffusivity), and other physical properties (such as dielectric constant and polarity) vary considerably with small changes in operating temperature, pressure, or both around the critical points. Hence, it is possible to fine tune a unique combination of properties necessary for a desired application. These unique processing capabilities of SCFs, long recognized and applied in the food industry, have recently been adapted to pharmaceutical applications.[11]

(2) Influence of Temperature: When we increases the temperature involves the absorption of heat and it increases the solubility of the drugs.

- If the dissolution of a component involves positive hit of solution, a rise in temperature leads to an increase in solubility of solid. Example is potassium nitrate in water.

-In other hand if the dissolution of a solid involves the liberation of heat then an increase in temperature leads to decrease in solubility. Example is calcium acetate in water.

(3) Influence of pH of the medium

Most of the drugs are weak electrolytes. The weak acids and weak bases undergo ionisation in solution. The ionised form of drugs are more soluble in water and unionised form of drugs are poorly water soluble. The extent of ionisation depends on the dissociation constant and the pH of the medium. For example, alkaloidal salts are more soluble in acidic pH and begin to precipitate as the pH increases. On the other hand, phenobarbitone is more soluble in alkaline pH and begins to precipitate as the pH decreases. The relationship between pH (of the preparation), solubility and pKa value of the drug is expressed as

Acidic drugs: pHp = pKa + log s-s0/ s0
Basic drugs: pHp = pKa + log s0/S- s0

Where pKa = dissociation constant of drug, s0 = solubility of unionised form, moles/litre, S= overall solubility of drug,moles/litre

If pH of the solution is known, solubility of drugs can be calculated using equations(1) and (2). Similarly minimum pH can be determined in order to maintain a solution of known concentration without precipitation.[12]

(4) Solid dispersion: Solid dispersion is widely used for increasing the absorption, dissolution and therapeutic effectiveness of drugs in dosage forms. Various techniques are use in SD described in **(Table -4)**"This technique can be defined as the distribution of one or more active ingredients (hydrophobic) in an inactive carrier or matrix (hydrophilic) at solid state. Solid dispersion mentions to a group of solid products containing of at least two different components, generally a hydrophobic drug and a hydrophilic matrix. These matrix can be either amorphous or crystalline. The drug can be isolated molecularly, in amorphous particles (clusters) or in crystalline particles. The mostly solvents used for solid dispersions includes methanol, water, ethanol, DMSO, chloroform, acetic acid. The most frequently used hydrophilic carriers for solid dispersions such as, *First Generation Carriers: Example: Crystalline carriers: Organic acids, Urea, Sugars.

*Second Generation Carriers: Fully synthetic polymers include polyethyleneglycols (PEG) andpovidone (PVP), polymethacrylates. Natural product based polymers aremainly used by cellulose derivatives, such as hydroxypropylmethyl cellulose (HPMC), orhydroxypropylcellulose, ethyl cellulose or such derivatives, such as cyclodextrins.

*Third Generation Carriers: Example: Surface active selfemulsifying carriers: Tween 80, poloxamer 408 andGelucire 44/14.[13]

Table 4 –Techniques of Solid Dispersion[15]

Method of SD Preparation	Substance used	Advantages	Mechanism
Fusion method	Poly ethylene glycol , Poly vinyl alcohol	Easy and Economical	Melting the drug within the carrier followed by cooling and pulverization of the obtained product.
Hot melting extrusion	Microcrystalline cellulose	Increase in stability and dissolution	With high speed extrusion of the drug & carrier, previously mixed, at melting temperature for a small period of time.
Solvent method	Tweens and poly vinyl pyrolidone	Lipophilic drugs are dissolved	Solubilizationof drug & carrier in volatile solvent that is later evaporate
Supercritical fluid method	CO_2 ,N_2	Increase in surface area of product	Dissolving drug & carrier in a solvent that is introduced into a particle formation vessel through a nozzle with simultaneously with CO_2.
Electrostatic spinning method	HPMC	Nanosized product	Liquid introduced in electric field & it produces fibers than drawn from liquid it forms fiber harden, which may involves mere cooling , chemical hardening or evaporation of solvent , & then harden fiber collected upon a suitably charged surface.
Freeze drying	Liquid N_2	Less thermal stress	Drying of dispersion in liquid nitrogen
Melt agglomeration	Ethyl cellulose and HPMC	Produce stable product	Mixing of drug in hot molten carrier

(5) Use of Surfactant: Surfactants are used for increase dissolution of drug. The basic mechanism behind this action of surfactant is that the wetting is firstly promoted so that penetration of dissolution fluid in to the solid drug particles can be increased. Various types of surfactants, ionic surfactants were preferred over others for better solubilizing agents. In most cases the anionic surfactants (such as sodium dodecyl sulphate) was found to give better results compare to cationic surfactant (such as cetyl trymethyl ammonium bromide) for solubility enhancement.

(6) Influence of Solvents: Water and vegetable are widely used as solvent in the formulation. The solubility of the drug is due to the polarity of the solvent that is dipole movement, hydrogen bonding between solute and

solvent is also essential. Therefore, structural features and presence of nonpolar and polar groups in the molecule are important. Influencing of solvent on solubility describe in **(Table-5).**

Table No -5: Influencing of solvent on solubility[16]

Solvent	Nature of Solute	Examples of Drugs	Dosage forms
Water(Polar)	Polar Substances	Vitamin B1&B2	Elixer
Water(Polar)	Strong Electrolytes	Sodium chloride	i.v. infusion
Water(Polar)	Weak Electrolytes	Sodium Phenobarbitone	Injection
Water(Polar)	Nonelectrolytes	Dextrose	i.v. injection
Oil(nonpolar)	Nonpolar substances	Progeteron	Oil injection

Poorly water soluble drugs are normally dissolved in non-aqueous vehicles such as liquid paraffin, arachis oil and ethyl oleate. In most cases, a mixture of solvents is used for maximum solubility of drugs.

(7) Influence of Co-solvents: A solute is more soluble in a mixture of solvents rather than in a single solvent. The solvents, which are used to increase the solubility of a drug in water, are called as co-solvents. This phenomenon is known as cosolvency. Ethanol, propylene glycol, glycerine, PEG 300, and PEG 400 (polyethylene glycols) are the commonly used cosolvents, because these are water miscible. This concept of cosolvency is used in the manufacture of liquid dosage forms such as syrups, elixirs, injections, creams and lotions for increase there solubility. Example of sovlents are benzyl alcohol, dimethyl sulphoxide (DMSO), Dimethyl acetamide (DMA) and Dimethyl formamide (DMF) used as supplementary solvents.[17]

(8)Change in dielectric constant of solvent: The co-solvent addition reduces dielectric constant of the solvent and increases solubility of hydrophobic molecules. Due to hydrogen bonding, water is a good solvent for polar molecules and has a high dielectric constant. The dielectric constant of a substance has energy needed to separate two oppositely charged groups. The energy required to separate two oppositely charged bodies is inversely proportional to the dielectric constant of the medium.

(9) Use of hydrates or solvates: Non stochiometric adducts involves entrapped solvent molecules with in the crystal lattice. A stoichiometric adduct, commonly referred to a solvate, is a molecular complex that has incorporated the crystallising solvent molecules within the crystal lattice. When the incorporated solvent is water, it is called as hydrate. A compound not containing any water within its crystal structure is termed anhydrous. Aqueous solubilities of anhydrous forms is higher than the hydrate forms.[18]

(10)Use of Soluble prodrug: It involves the incorporation of polar or ionisable moiety (inactive form) into the parent compound to improve aqueous solubility. This is successfully used to imrove water solubility of corticosteroids, vitamins and benzodiazepines. For example. of morphine s more soluble after subsequent cleavage of the acetyl groups by hydrolysis yields morphine (heroin).

(11)Salt formation: This is used to enhance the dissolution rate of drugs because dissolution rate of particular salt is usually different from that of parent compound. For example, sodium and potassium salt of week acid dissolve more rapidly than that of pure salt. Limitation of this technique includes epigastric distress due to high alkalinity, reactivity with atmospheric water and carbon dioxide leads to precipitation, and patient compliance.[19]

(12)Cryogenic Techniques: Cryogenic techniques have been used to enhance the dissolution rate of drugs by creating nanostructured amorphous drug particles at low temperature. Cryogenic can be defined as the type of injection device (capillary, rotary, pneumatic, and ultrasonic nozzle), location of nozzle (above or under the liquid level), and the composition of cryogenic liquid (hydrofluoroalkanes, N_2, Ar, O_2, and organic solvents). After cryogenic processing, various drying processes like spray freeze drying, atmospheric freeze drying, vacuum freeze drying, and lyophilisation, dry powder is obtained.[20]

(13)Hydrotrophy: Hydrotrophy is a process, in which large amount of second solute added, the hydrotropic agent results in an increase in the aqueous solubility of first solute. Ionic organic salts are hydrotropic agent, consists of alkali metal salts of various organic acids.[21] Additives or salts which can increase solubility in given solvent are said to be "salt in" the solute and those salts that decrease solubility "salt out". "salting in" of nonelectrolytes called "hydrotropic salts"; a phenomenon known as "hydrotropism." Hydrotrophy designed for the increase in solubility in water due to the presence of large amount of additives.
The classification on the basis of molecular structure is difficult. Specific examples of hydrotrophes are ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, α and β-naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate).[22]

(14)Modification of the crystal habit: Polymorphism is ability of compound to crystallize is more than one crystalline form. Different polymorph of drugs having

different physicochemical properties such as solubility, melting point, density, texture and stability. poltmorphs can be classified as enantiotropes and monotropes. This classification based on thermodynamic properties. One polymorphs form can reversibly change into another at a definite transition temperature below its melting point in case of enantiotropic system, while in case of monotropes there is no reversible transition. Once the drug or compound charecterized under one of those category, further study involves detection of metastable form. Metastable form having higher solubility due to higher energy. Also the amorphous forms of drugs are more suitable due to higher solubility and higher energy. Solubility of these different forms in decreasing order- Amorphous >Metastable polymorph >Stable polymorph.[23]

(15)Microemulsions: The term microemulsion was first described by Jack H. Shulman in 1959. It is a four component system composed of external phase, internal phase, surfactant and cosurfactant. By the addition of surfactant and cosurfactant, it results in the formation of an optically clear, isotropic, thermodynamically stable emulsion which is termed as microemulsion because the diameter of the internal or dispersed phase droplet is < 0.1 μ droplet. There is no external energy required as in case of coarse emulsions. The surfactant and the cosurfactant form a mixed film at the interface, which contributes to the stability of the microemulsions.

Advantages of microemulsion over coarse emulsion- preparation is very easy due to spontaneous formation, thermodynamic stability, transparent and elegant appearance, increased drug loading, enhanced penetration through the biological membranes, increased bioavailability.

(16) Co-crystallisation: This is the new method for the enhancement of drug solubility is through the application of the co-crystals, it is also referred as molecular complexes. If the solvent is an integral part of the network structure and forms at least two component crystal, then it may be termed as co-crystal .Co-crystal is defined as a crystalline material that consists of two or more molecular species which held together by non-covalent forces. Co-crystals are more stable, mostly the co-crystallizing agents are solids at room temperature. Co-crystallizing agents are classified only in three as generally recognized as safe (it includes saccharin, nicotinamide and acetic acid limiting the pharmaceutical applications.

Co-crystallisation between two active pharmaceutical ingredients has also been reported. This may require the use of subtherapeutic amounts of drug substances such as aspirin or acetaminophen.

Preparation of co-crystals by evaporation of a heteromeric solution or by grinding the components together. Another technique used for the preparation of co-crystals includes sublimation, growth from the melt, and slurry preparation.[24]

7. CONCLUSION

This article concludes that, solubility is the most important factor that controls the formulation of the drug as wel las therapeutic efficacy, bioavailability of the drug. Dissolution of drug is the rate determining step for oral absorption of the poor water soluble drugs and solubility is a basic requirement for the formulation and development of different dosage form.

Solubility is a important factor to reach the systemic circulation to show its pharmacological response. A lot of research has been carried out in this area and for better clinical efficiency, some improvements in solubility and dissolution rate. The currently available technologies are used to enhance the solubility and dissolution to maximize the bioavailability and therapeutic efficacy. A study of solubility also resulting information about the structure and inter-molecular forces of component. Use of solubility characteristics is for enhancement of bioavailability, pharmaceutical actions and but solubility enhancement of various poorly soluble drugs is a challenging task for researchers and pharmaceutical scientists.

The various techniques described above alone or in combination can be used to enhance the solubility. Proper selection of solubility enhancement method is the key to ensure the goals of a good formulation such as good oral bioavailability, reduce frequency of dosing and better patient compliance combined with a low cost of production. Selection of method depends upon some drug characteristics like solubility, chemical nature, melting point, absorption site, physical nature, pharmacokinetic behavior and dosage form requirement like tablet or capsule formulation, strength, immediate, or modified release and also some regulatory requirements like maximum daily dose of any excipients and/or drug, approved excipients, analytical accuracy and so forth.

Currently only 8% of new drug can have both high solubility and permeability (class one drug of BCS classification). Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. Although many of techniques like salt formation, particle size reduction, etc. have commonly been used to increase dissolution rate of the drug, there are practical limitation with these techniques the desired bioavailability enhancement may not always be achieved. Solid dispersion is mainly used to mask the taste of the drug substances, and to prepare rapid disintegration oral tablets

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