International Journal of Universal Pharmacy and Bio Sciences 10(6): November-December 2021

INTERNATIONAL JOURNAL OF UNIVERSAL PHARMACY AND BIO SCIENCES

IMPACT FACTOR 4.018*

ICV 6.16*

Pharmaceutical Sciences **Review Article……!!!**

REVIEW ON :"SOLUBILITY ENHANCEMENT TECHNIQUES FOR POORLY SOLUBLE DRUGS"

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KEYWORDS:

Drug Solubility, Bioavailability, BCS Classification, Micronization, Nanonization, Sonocrystallization, Spray freezing.

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ABSTRACT

Solubility, the phenomenon of dissolution of solute in solvent to give a homogenous system, is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired (anticipated) pharmacological response. Insufficient dissolution rate of the drug is the limiting factor in the oral bioavailability of poorly water soluble compounds. This review discusses BCS classification, carriers for solubility enhancement and different techniques for solubility enhancement.Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include micronization, nanonization, sonocrystallization, supercritical fluid method, spray freezing into liquid and lyophilization, evaporative precipitation into aqueous solution, use of surfactant, use of co-solvent, hydrotropy method, use of salt forms, solvent deposition, solubilizing agents, modification of the crystal habit, co-crystallisation, complexation and drug dispersion in carriers.Selection of solubility improving method depends on drug property, site of absorption, and required dosage form characteristics.With the advent of combinatorial chemistry and a high throughput screening, the number of poorly water soluble compounds has increased solubility.

INTRODUCTION:

Definition of Solubility: Solubility is the ability of a solid, liquid, or gaseous chemical substance (referred to as the solute) to dissolve in solvent (usually a liquid) and form a solution. Solubility does not depend on particle size; given enough time, even large particles will eventually dissolve.

Solubility is usually expressed in terms of concentration (mass/ volume) to describe a solute's ability to homogenously dissolve in a solvent[3]. The solvent is generally a liquid, which can be a pure substance or a mixture of two liquids. One may also speak of solid solution, but rarely of solution in a Gas.The extent of solubility ranges widely, from infinitely soluble (fully miscible) such as ethanol in water, to poorly soluble, such as silver chloride in water. The term insoluble is often applied to poorly or very poorly soluble compounds [4].

Solubility is not to be confused with the ability to dissolve or liquefy a substance, since these processes may occur not only because of dissolution but also because of a chemical reaction. For example, zinc is insoluble in hydrochloric acid, but does dissolve in it by chemically reacting into zinc chloride and hydrogen, where zinc chloride is soluble in hydrochloric acid. Solubility does not also depend on particle size or otherkinetic factors; given enough time, even large particles will eventually dissolve [5]. The intestinal permeability classification is based on a comparison to the intravenous injection. All those factors are highly important, since 85% of the most sold drugs in the USA and Europe are orally administered.

All drugs have been divided into four classes:

class I	High soluble and High permeable
class II	Low soluble and High permeable
class III	Low soluble and High permeable
class IV	Low soluble and Low permeable

Table :-1 CLASSIFICATION OF DRUGS

Importance of Solubility:

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, costeffectiveness, least sterility constraints, and flexibility in the design of dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug products [6].Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic

development. The negative effect of compounds with low solubility include poor absorption and bioavaila[7].

Factors Affecting Solubility:

1) Temperature:

The solubility of a given solute in a given solvent typically depends on temperature. For many solids dissolved in liquid water, solubility tends to correspond with increasing temperature. As water molecules heat up, they vibrate more quickly and are better able to interact with and break apart the solute.Solubilty of various substances vs. temperature change Solubility increases with temperature for most substances; for example, more sugar will dissolve in hot water than in cold water.The solubility of gases displays the opposite relationship with temperature; that is, as temperature increases, gas solubility tends to to decreased. In a chart of solubility vs temperature, notice how solubility tends to increase with increasing temperature for the salts and decrease with increasing temperature for the gases.

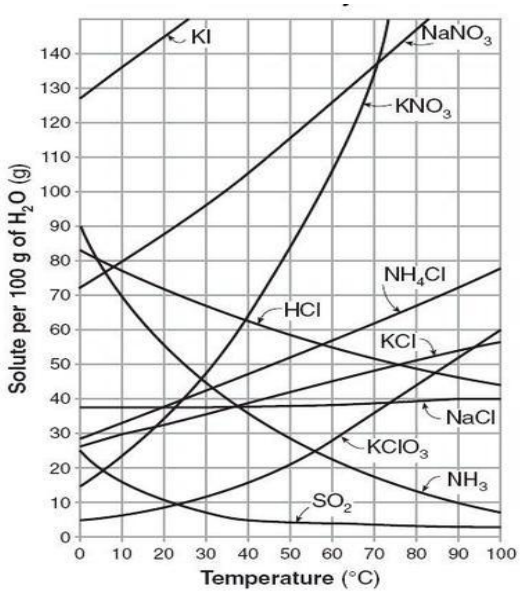

Fig- 1: Temperature Vs Solute per 100 g of H_2O(gm)

2) Pressure:

Pressure has a negligible effect on the solubility of solid and liquid solutes, but it has a strong effect on solutions with gaseous solutes. This is apparent every time you open a soda can; the hissing sound from the can is due to the fact that its contents are under pressure, which ensures that the soda stays carbonated (that is to say, that the carbon dioxide stays dissolved in solution). The takeaway from this is that the solubility of gases tends to correlate with increasing pressure[8].

Henry's law :

Henry's law is one of the gas laws formulated by William Henry in 1803 and states: "At a constant temperature, the amount of a given gas that dissolves in a given type and volume of liquid is directly proportional to the partial pressure of that gas in equilibrium with that liquid." An equivalent way of stating the law is that the solubility of a gas in a liquid is directly proportional to the partial pressure of the gas above the liquid:

$$C=kP_{gas}$$

where, C is the solubility of a gas at a fixed temperature in a particular solvent (in units of M or mL gas/L)

k is Henry's law constant (often in units of M/atm)

Pgas is the partial pressure of the gas (often in units of atm)

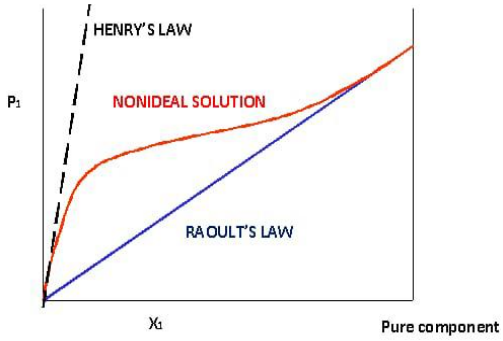

Fig-2 : Positive non-ideal behavior of the vapor pressure of a solution follows Henry's Law at low concentrations and Raoult's Law at high concentrations (pure).

Application of Henry's law :

1) Henry's law only works if the molecules are at equilibrium.
2) Henry's law does not work for gases at high pressures (e.g., N2(g) at high pressure becomes very soluble and harmful when in the blood supply).
3) Henry's law does not work if there is a chemical reaction between the solute and solvent (e.g., HCl(g) reacts with water by a dissociation reaction to generate H3O+ and Cl− ions)[9].

Limitations of Henry's law:

The pressure should be low and the temperature should be high i.e the gas should behave like an ideal gas.

The gas should not undergo compound formation with the solvent or association or dissociation in the solvent.[10].

3) Polarity:

A popular saying used for predicting solubility is “Like dissolves like.” This statement indicates that a solute will dissolve best in a solvent that has a similar chemical structure; the ability for a solvent to dissolve various compounds depends primarily on its polarity. For example, a polar solute such as sugar is very soluble in polar water, less soluble in moderately polar methanol, and practically insoluble in non-polar solvents such as benzene. In contrast, a non-polar solute such as naphthalene is insoluble in water, moderately soluble in methanol, and highly soluble in benzene[8].

4) Solubility Chart:

The solubility chart shows the solubility of many salts. Salts of alkali metals (and ammonium), as well as those of nitrate and acetate, are always soluble. Carbonates, hydroxides, sulfates, phosphates, and heavy metal salts are often insoluble.

Solubility chart: The solubilities of salts formed from cations on the left and anions on the top are designated as: soluble (S), insoluble (I), or slightly soluble (sS).SolubilitySolubility of salt and gas solutes in liquid solvent.[8]

	Bromide Br^-	Carbonate CO_3^{2-}	Chloride Cl^-	Chlorates ClO_3^-	Hydroxide OH^-	Nitrate NO_3^-	Oxide O^{2-}	Phosphate PO_4^{3-}	Sulfate SO_4^{2-}	Dichromate $Cr_2O_7^{2-}$
Aluminium Al^{3+}	S	X	S	S	I	S	I	I	S	I
Ammonium NH_4^+	S	S	S	S	S	S	X	S	S	S
Calcium Ca^{2+}	S	I	S	S	sS	S	sS	I	sS	I
Copper(II) Cu^{2+}	S	I	S	S	I	S	I	I	S	I
Iron(II) Fe^{2+}	S	I	S	S	I	S	I	I	S	I
Iron(III) Fe^{3+}	S	X	S	S	I	S	I	I	sS	I
Magnesium Mg^{2+}	S	I	S	S	I	S	I	I	S	I
Potassium K^+	S	S	S	S	S	S	S	S	S	S
Silver Ag^+	I	I	I	S	X	S	I	I	sS	I
Sodium Na^+	S	S	S	S	S	S	S	S	S	S
Zinc Zn^{2+}	S	I	S	S	I	S	I	I	S	I
	Bromide Br^-	Carbonate CO_3^{2-}	Chloride Cl^-	Chlorates ClO_3^-	Hydroxide OH^-	Nitrate NO_3^-	Oxide O^{2-}	Phosphate PO_4^{3-}	Sulfate SO_4^{2-}	Dichromate $Cr_2O_7^{2-}$

Fig - 3

Solubilization:

Solubilization is the formation of a thermodynamically stable, isotropic solution of a substance (the solubilizate), normally insoluble or slightly soluble in water, by the addition of a surfactant (the solublizer). The micelles of the surfactant cause solubilization of the substrate, producing an isotropic solution of the chemical. The solubilizate can be incorporated in the surfactant micelle in different ways, depending on the nature of the substrate and the surfactant micelles.

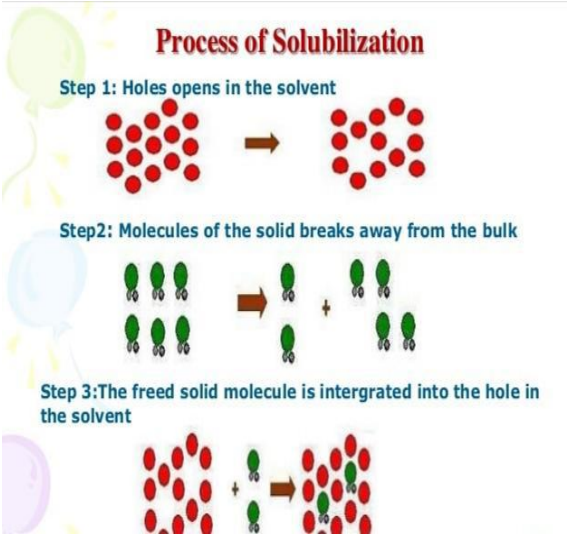

Fig- 4

For hydrophobic substrates, the molecules become incorporated in the hydrocarbon core of the micelle. With more polar substrates, the molecules may become incorporated in the hydrophilic PEO chains of the micelle or they may be simply adsorbed at the micelle surface[11] .

"SOLUBILITY ENHANCEMENT TECHNIQUES FOR POORLY SOLUBLE DRUGS" :

Solubility of active pharmaceutical ingredients (API's) has always been a concern for formulators, since inadequate aqueous solubility may hamper development of products and limit bioavailability of oral products. Solubility plays an essential role in drug disposition, since the maximum rate of passive drug transport across the biological membrane, the main pathway for drug absorption is a product of permeability and solubility.

Various technologies have arisen to meet the challenge posed by insoluble compounds and these technologies have made a different too. The techniques that are used to overcome poor drug solubility:

1) Physical Modification

2) Chemical Modifications

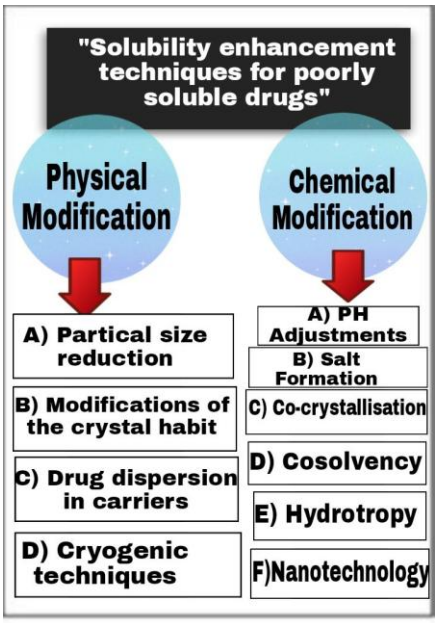

Fig-5

1) Physical Modification

A) Particle Size Reduction:

Particle size reduction: Particle size reduction can be achieved by
a) Micronization
b) Nanosuspension
c) Sonocrystalisation
d) Supercritical fluid process Colloid mill.

Table :-2 PARTICLES SIZE REDUCTION : PARTICLE SIZE REDUCTION METHOD

The solubility of drug is often intrinsically related to drug particle size; as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows greater interaction with the solvent which causes an increase in solubility.Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. Particle size reduction is thus permitting an efficient, reproducible, and economic means of solubility enhancement. However, the mechanical forces inherent to comminution, such as milling and grinding, often impart significant amounts of physical stress upon the drug product which may induce degradation. The thermal stress which may occur during comminution and spray drying is also a concern when processing thermosensitive or unstable active compounds[12].

Theories for partical size reduction techniques:

1) ***Griffith theory*** :

Amount of force to be applied is dependant on the crack length and focus of stress at the atomic bond of the crack apex.

2) Kick's law:

Size reduction of a given quantity of material is constant t for the same reduction ratio regardless of the original size[13].

3) Rittinger's law:

Particulate size reduction is directly proportional to the new surface produced.

4) Bond's law: Reduces particle size is proportional to the square root of the diameter of the particle produced.

a) Micronization:

Micronization increases the dissolution rate of drugs through increased surface area. • Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. • Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug [14].

b) Nanosuspension :

Nanosuspension technology has been developed as a promising candidate for efficient delivery of hydrophobic drugs. This technology is applied to poorly soluble drugs that are insoluble in both water and oils. A pharmaceutical nanosuspension is a biphasic system consisting of nano sized drug particles stabilized by surfactants for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm [15, 16].

Advantage of Nanosuspension:

1) Increase resistance to hydrolysis and oxidation.

2) Increase physica stability to agglomerate formation.

3)Reduction in injection volumes; essential for intramuscular, subcutaneous, & intraocular/ ophthalmic drugadministration.

4)Increased excipient compatibility.

5)Ease of manufacture and scale-up.

6)Long-term physical stability and versatility.

7)Increased oral absorption.

Disadvantages for nanosuspension drug delivery:

1)Uniform and efficacious doses cannot be achieved.

2) Improper dose administration or location.

3)Special care must be taken during handling in a manufacturing plant and material transportation.

4)Physical stability, sedimentation and compaction are common drawbacks[13].

c) Sonocrystalisation :

Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size. Sonocrystallisation utilizes ultrasound power characterised by a frequency range of 20–100 kHz for inducing crystallisation. It not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients. Most applications use ultrasound in the range 20 kHz-5 MHz[17].

d) Supercritical fluid process :

Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp), allowing it to assume the properties of both a liquid and a gas. At near-critical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power. Once the drug particles are solubilised within SCF, they may be recrystallized at greatly reduced particle sizes[18, 19].

B) Modification of the crystal habit:

Polymorphs Enantiotropic One polymorphs form can change reversibly into another at a definite transition temperature below the melting point. Monotropic No reversible transition is possible. Metastable forms are associated with higher energy and thus higher solubility. Similarly the amorphous form of drug is always more suited than crystalline form due to higher energy associated and increased surface area. The anhydrous form of a drug has greater solubility than the hydrates. This is because the hydrates are already in interaction.

the order for dissolution of different solid forms of drug is Amorphous > metastable polymorph > stable polymorph • Melting followed by a rapid cooling or recrystallization from different solvents can produce metastable forms of a drug.

C) Drug dispersion in carriers:

The term “solid dispersions” refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the

a) Hot melt mehod
b) Solvent evaporation method
c) Hot melt extrusion

Table :- 3 Drug Dispersion method

a) Hot melt method

Drug + vehicle (m.p low, organic solvent – insoluble) A molecular dispersion can be achieved or not, depends on the degree of supersaturation and rate of cooling used in the process. (heating) Melting . Freezing quickly Dosage forms Important requisites :

1. Miscibility of the drug & carrier in the molten form,
2. Thermostability of the drug & carrier. Suitable to drugs and vehicles with promising heat stability.

b) Solvent evaporation method:

Drug + vehicle (both soluble in solvent) organic solvent solution evaporate the solvent coprecipitates dosage forms The solvent evaporation can be done by spray drying or freeze drying. Temperatures used for solvent evaporation generally lie in the range 23-65 C. suitable to drugs with volatility or poor stability suitable to drugs with volatility or poor stability.

c) Hot-melt Extrusion:

Hot melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of an immiscible component leads to amorphous drug dispersed in crystalline excipient. The process has been useful in the preparation of solid dispersions in a single step.

D) Cryogenic Techniques:

Cryogenic techniques have been developed to enhance the dissolution rate of drugs by creating nanostructured amorphous drug particles with high degree of porosity at very low-temperature conditions. Cryogenic inventions can be defined by 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, N2, Ar, O2 and organic solvents). After cryogenic processing, dry powder can be obtained by various drying processes like spray freeze drying, atmospheric freeze drying, vacuum freeze drying, and lyophilisation.

Spray Freezing onto Cryogenic Fluids:

Briggs and Maxvell invented the process of spray freezing onto cryogenic fluids. In this technique, the drug and the carrier (mannitol, maltose, lactose, inositol, or dextran) were dissolved in water and atomized above the surface of a boiling agitated fluorocarbon refrigerant.

Spray Freezing into Cryogenic Liquids (SFL):

The SFL particle engineering technology has been used to produce amorphous nanostructured aggregates of drug powder with high surface area and good wettability.

Spray Freezing into Vapor over Liquid (SFV/L):

Freezing of drug solutions in cryogenic fluid vapours and subsequent removal of frozen solvent produces fine drug particles with high wettability.

Ultra-Rapid Freezing (URF):

Ultra-rapid freezing is a novel cryogenic technology that creates nanostructured drug particles with greatly enhanced surface area and desired surface morphology by using solid cryogenic substances [20,21,22,23].

2) Chemical modifications for solubility enhancement:

A) **PH Adjustment:**

For organic solutes that are ionizable, changing the pH of the system may be simplest and most effective means of increasing aqueous solubility. Under the proper conditions, the solubility of an ionizable drug can increase exponentially by adjusting the pH of the solution. A drug that can be efficiently solubilized by pH control should be either weak acid with a low pKa or a weak base with a high pKa.Furosemide (pKa of 3.9) is unstable at an acid pH, but is very stable under alkaline conditions. In dogs, the oral bioavailability is approximately 77%.

B) Salt formation:

Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. It can lead to changes in solubility and permeability of the parent molecule, which can lead to improved bioavailability. The use of salt forms is a well known technique to enhance dissolution rates. Generally, an alkaloidal base is slightly soluble in water, but if the pH of medium is reduced by addition of acid, the solubility of the base is increased as the pH continues to be reduced. Example: Rosiglitazone maleate, Pioglitazone HCl, Atropine sulphate.

C) **Co-crystallisation:**

Co crystals are defined as crystalline complexes of two or more neutral molecular constituents bound together in the crystal lattice through non covalent interactions. Cocrystallization is a flourishing research field with direct application to the pharmaceutical industry.The new approach available 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. If the solvent does

not participate directly in the network itself, as in open framework structures, then it is termed as clathrate (inclusion complex). A co-crystal may be defined as a crystalline material that consists of two or more molecular (and electrically neutral) species held together by non-covalent forces.

Different techniques for co crystallization :

1)Solvent evaporation 2)Grinding 3)Slurry Co - Crystallization 4)Solvent drop grinding (Modification of Grinding) 5)High throughput co-crystallization 6)Hot melt extrusion 7) Sonocrystallization Method. Few example of research work done cocrystal formation Flurbiprofen, Itraconazole ,Carbamazepine etc.

Co-Crystals Characterization Parameters:

1) Solubility 2) Maximum wavelength 3) Stability 4) Intrinsic dissolution 5) Bioavailability 6) Melting Point 7) Melt (Hot stage microscopy) 8) DSC 9) XRD 10) Vibrational spectroscopy.

D) **Cosolvency:**

The solubility of a poorly water soluble drug can be increased frequently by the addition of a water miscible solvent in which the drug has good solubility known as Co solvent.Co-solvents are mixtures of water and one or more water miscible solvents used to create a solution with enhanced solubility for poorly soluble compounds. Co-solvent formulations of poorly soluble drugs can be administered orally and parenterals. The pharmaceutical form is always liquid. Poorly soluble compounds which are lipophilic or highly crystalline that have a high solubility in the solvent mixture may be suited to a co-solvent approach. Commonmly used cosolvents Glycerol, propylene glycol, PEG 400, Dimethyl Sulfoxide, Dimethyl Acetamide, Ethanol, n-Octanol are the commonly used cosolvents. Ideal behaviour of Cosolvents It should be easily available and sufficiently pure.It should be non-toxic, non-irritating, and nonsensitizing. It also must exert no pharmacologic activity of its own. It should be stable under normal conditions of pharmaceutical use.It should not adversely affect the action of the medicament. Ideal solvent should not be affected by acids or alkalies. The viscosity of solvent should be as such so as to allow ease of administration.It should remain fluid over a wide temperature range.

E) **Hydrotropy:**

Hydrotropy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of another solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water-soluble drugs. Significance of Hydrotrophy. Hydrotropy is suggested to be superior to other solubilization method, such as miscibility, micellar solubilization, co solvency and salting in,

because the solvent character is independent of pH, has high selectivity and does not require emulsification. It only requires mixing the drug with the hydrotrope in water and do not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system. Solvent character is independent of pH, hydrotrophy has high selectivity and does not require emulsification.

F) Use of novel solubilizer:

The solubility of poorly soluble drug can also be improved by various solubilizing materials. Ex. Conventional solubilizer Polysorbates, PEG 400 Sepitrap,Soluplus Povacoat, dendrimers, is improve the solubility of hydrophobic API

G) **Nanotechnology:**

Nanotechnology can be used to improve solubility. Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometers (nm) or less. For many new chemical entities of very low solubility, oral bioavailability enhancement by micronisation is not sufficient because micronized product has the tendency of agglomeration, which leads to decreased effective surface area for dissolution and the next step taken was Nanonisation[24].

Conclusion :

1) For beneficial effect of Orally administered drugs, solubility is rate limiting parameters achieve desired concentration in systemic circulation.
2) Solubility of drug important factor for formulation and therapeutic effect of drug.
3) Various Techniques described in review may be used alone or combined with other to enhance solubility of poorly soluble drugs.
4) Selection of solubility enhancement techniques is important for formulation such as :

Good oral bioavailability, reduced dosing frequency low production cost.

5) selection of appropriate solubility enhancement techniques is dependent on drug Characteristics.

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