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REVIEW ARTICLE

A RECENT TRENDS IN ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF POORLY SOLUBLE HYDROPHOBIC DRUGS BY USING PHYSICAL AND CHEMICAL MODIFICATIONS

***Malak Azhar Hameed[1], Sayyed Nazim[1], Tarique khan[1], Md. Rageeb Md. Usman[2]**

[*1]Department of Pharmaceutics, Ali Allana College of Pharmacy, Akkalkuwa, Maharashtra, India

[3]Department of Pharmacognosy, Smt. S. S. Patil College of Pharmacy, Chopda, Maharashtra, India

ABSTRACT

The aim of this review was to improve the solubility and bioavailability of poorly soluble drugs by using various approaches like physical, chemical and others modifications or techniques. The ability to increase aqueous solubility can thus be a valuable aid to increasing efficiency and/or reducing side effects for certain drugs. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown which is defined as maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. Drug with poor water solubility cause slow dissolution rates, generally show erratic and incomplete absorption leading to low bioavailability when administered orally. This is true for parenterally, topically and orally administered solutions. Among all newly discovered chemical entities about 40% drugs are lipophillic and fail to reach market due to their poor water solubility. Hence this review was to described in detailed solubility, process of solubilization, factor affecting solubilization, and various recent technique used for improvement of solubility such as GAS, RESS, Nanosuspension Micro emulsion, Use of salt form of drug, micronisation, SCF, Inclusion complex, Co-solvancy Solid Dispersion.

KEYWORDS: Solubility enhancement, Poorly water soluble, solid dispersion, Techniques.

INTRODUCTION:

SOLUBILITY:

Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature and in qualitative terms, it may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug may be expressed as parts, percentage, molarity, molality, volume fraction, and mole fraction[1]. The substance to be dissolved is called as solute and the dissolving solution in which the solute dissolve is called as solvent, which at equilibrium to form a solution. The process of dissolving solute into solvent is called as solution or hydration if the solvent is water[2]. The diffusion of molecules or ions from a solid state into solution is known as dissolution. In general, when a drug dissolves, solid molecule or ion are transfer from solid state to liquid solution and mix molecule by molecule with the liquid and appear to become part of that liquid. Therefore, drug dissolution is the process by which drug molecules are transfer from a solid surface and enter into a solution phase. There are the various drawback associate with the use of poorly soluble drugs such as increasing the dosage, administration frequency and the resultant occurrence of side effects. To overcome this problem of poorly water soluble drugs there are numerous approaches are available and reported in literature to enhance the solubility of poorly water soluble drugs. The techniques are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected and nature of intended dosage form[3]. This review is intended to discuss the process of solubilization, factor affecting solubilization and various traditional and novel techniques for solubility enhancement of hydrophobic drugs for oral pharmaceutical formulation.

The following Table 1 show solubility chart in which various descriptive terms are described as how much part of solvents required dissolving one part of solute. The solubility of a drug may be expressed as parts, percentage, molarity, molality, volume fraction, and mole fraction.

Table: 1 showing expression for approximate solubility[4]

Descriptive terms	Relative amounts of solvents to dissolve1 part of solute
Very soluble	Less than 1
Freely soluble	From 1-10

*Corresponding author: Malak Azhar Hameed

Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000-10,000
Insoluble or practically Insoluble	More than 10,000

PROCESS OF SOLUBILIZATION:

The process of solubilization involves the breaking of intermolecular or inter-ionic 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 the solute molecule or ion[5] Solubilization process occurs into three steps.

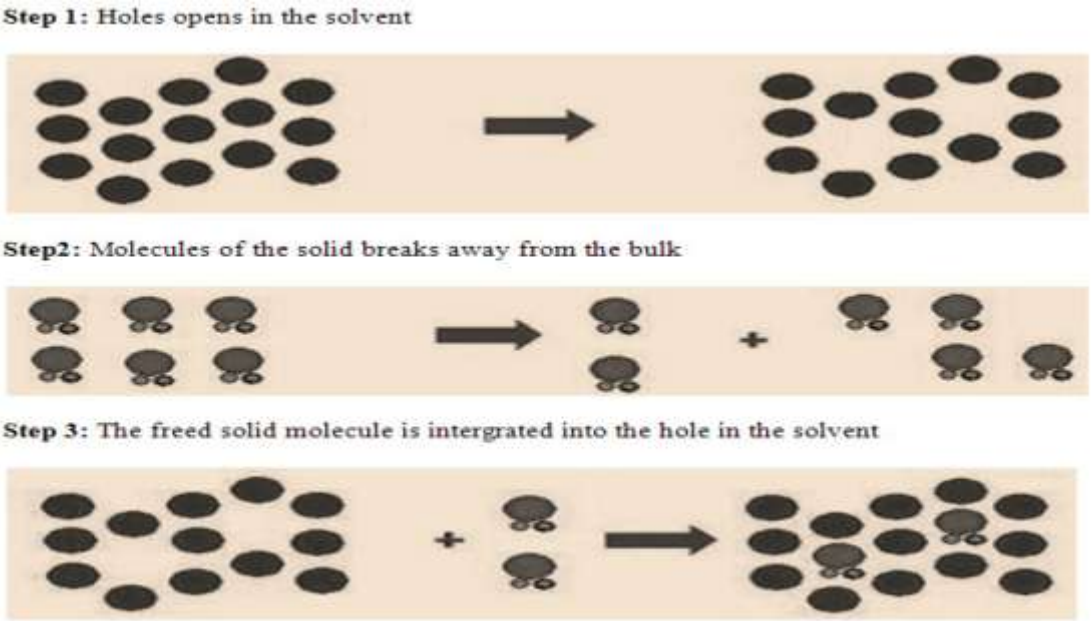


Fig. 1 Process of solubilisation

Figure 1: Step of solubilization

The first step involve in the solubilization process is hole open in the solvent. It provide cavity within the solvent molecule for the solute ion or molecule. The second step is that the molecule of solute breaks away from the bulk in to the solution and in the third step the freed solid molecule is integrated in to hole in the solvent [6, 7].

FACTOR AFFECTING SOLUBILIZATION PROCESS: [8, 61]

The solubility depends on the nature and composition of solvent medium, the physical form of the solid as well as temperature and pressure of system. Consider a lot of factor, which affects the solubility like

1. Particle size
2. Temperature
3. Pressure
4. Nature of the solute and solvent
5. Molecular size
6. Polarity
7. Polymorphs
8. Rate of solution

TECHNIQUES OF SOLUBILITY ENHANCEMENT:

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are[8].

1. PHYSICAL MODIFICATIONS:

A. Particle Size Reduction

- Supercritical fluid process
- Sonocrystalisation
- Micronization
- Nanosuspension

B. Modification of the Crystal Habit

- Polymorphs
- Pseudo polymorphs

C. Drug Dispersion in Carriers

- Eutectic mixtures
- Solid dispersions
- Solid solutions

D. Complexation

- Use of complexing agents

E. Solubilization by Surfactants:

- Micro emulsions
- Self micro emulsifying drug delivery systems

2. Chemical Modifications

3. Other Methods

- Hydro trophy
- Nanotechnology
- Co solvency
- Cocrystalisation
- Use of soluble prodrug
- Self micro emulsifying drug delivery

PHYSICAL MODIFICATIONS:

Particle size reduction: Particle size reduction can be achieved by micronisation and Nanosuspension, Sonocrystalisation and Supercritical fluid process. Each technique utilizes different equipment's for reduction of the particle size.

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[9,10]. Once the drug particles are solubilized within SCF, they may be recrystallized at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows micronisation of drug particles within narrow ranges of particle size, often to sub-micron levels. Current SCF processes have demonstrated the ability to create nanoparticulate suspensions of particles 5-2,000nm in diameter[11, 12]. There are various SCF process such as precipitation with compressed antisolvants process (PCA), solution enhanced dispersion by SCF (SEDS), and supercritical antisolvants processes (SAS), Rapid Expansion of Supercritical Solutions (RESS), Gas Anti Solvent Recrystallization (GAS) and aerosol supercritical extraction system (ASES) [13].

RAPID EXPANSION OF SUPERCRITICAL SOLUTIONS:

In Rapid Expansion of Supercritical Solutions process the supercritical solvent saturated with a solute is allowed to pass through nozzle at a very rapid rate, causing the precipitation of the solute. This process is also known as supercritical fluid nucleation (SFN). This process induces rapid nucleation of the supercritical fluid dissolved drugs and surfactants resulting in particle formation with a desirable size distribution in a very short time. The surfactants in the supercritical fluid stabilize the newly formed small particles and suppress any tendency of particle agglomeration or particle growth when spraying this solution (drug + surfactant + CO2) into an aqueous solution containing a second surface modifier[14]. The SF dissolves and gets saturated with the solute, and the resultant solution is introduced into a precipitation chamber by expansion through capillary or laser-drilled nozzle. During expansion or decompression phase, the density and solubilizing power of the SF decreases dramatically, resulting in a high degree of solute super saturation and subsequent precipitation[15].

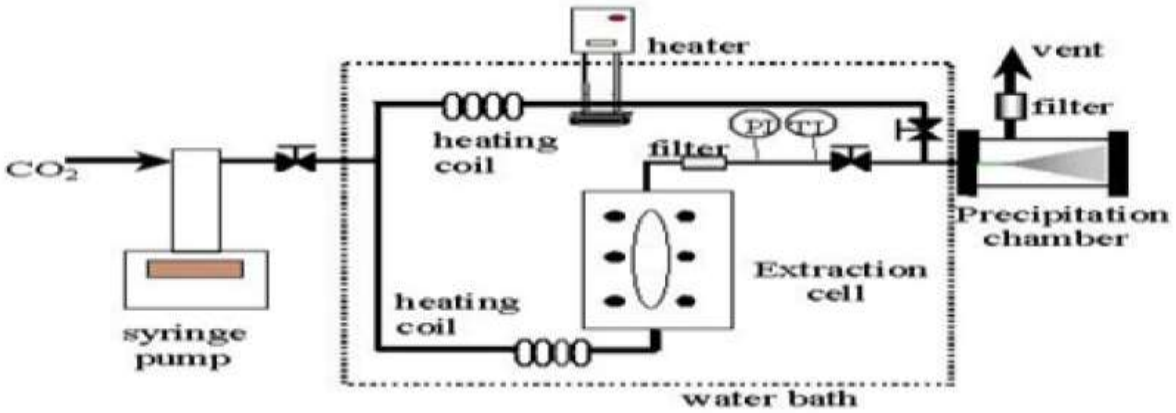


Figure 2: Rapid Expansion of Supercritical Solutions

GAS ANTISOLVANT RECRYSTALLIZATION:

It is a well-known method that a poor solvent of a particular solute can be added to the solution to precipitate the solute. This is called salting out and is widely used for crystallization purposes. However, disadvantages of this technique include poor control over the precipitated crystal morphology, size distribution and presence of residual solvents[16].

SONOCRYSTALLISATION:

The new technique for particle size reduction on the basis of crystallization by using ultrasound is Sonocrystallisation. This technique utilizes ultrasound power characterized by a frequency range of 20–100 kHz for inducing crystallization. Recrystallization of poorly soluble materials using liquid solvents and antisolvants has also been employed successfully to reduce particle size[17]. It's 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.

MICRONIZATION:

Smaller particle size may increase surface area and improves the dissolution properties of the drug. General methods of particle size reduction, such as milling and spray drying, rely upon mechanical stress to disaggregate the active compound. The micronisation is used to increased surface area for dissolution[18]. The solubility of drug is related to drug particle size. Micronisation increases the dissolution rate of drugs through increased surface area; it does not increase equilibrium solubility[19]. Micronization of drugs is done by milling techniques using jet mill, ball mill, and hammer mills etc. these techniques cannot be used for some drug having photosensitive and alteration of physiochemical properties by use of these mills.

NANOSUSPENSION:

A pharmaceutical Nano-suspension is biphasic systems consisting of nano sized drug particles stabilized by surfactants for either oral and topical use or parenteral and pulmonary administration. Nano-suspension technology has been developed as a promising candidate for efficient delivery of hydrophobic drugs[20]. This technology is applied to poorly soluble drugs that are insoluble in both water and oils. The particle size distribution of the solid particles in nano-suspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm [21].

SOLUTION ENHANCED DISPERSION BY SUPERCRITICAL FLUID:

The drug solution and the SF are introduced simultaneously into the arrangement causing rapid dispersion, mixing and Extraction of the drug solution solvent by SF leading to very high super saturation ratios. This technique was developed at the University of Bradford to minimize some of the limitations of the RESS and GAS methods. The drug solution and the SF are introduced simultaneously into the arrangement causing rapid dispersion, mixing and Extraction of the drug solution solvent by SF leading to very high super saturation ratios. The temperature and pressure together with accurate metering of flow rates of drug solution and SF through a nozzle provide uniform condition for particle formation[22].

MODIFICATION OF THE CRYSTAL HABIT:

Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubility's. Generally the range of solubility differences between different polymorphs is only 2-3 folds due to relatively small differences in free energy[23].

DRUG DISPERSION IN CARRIERS:

EUTECTIC MIXTURE:

The eutectic mixture means that the easily melted, eutectic mixture is a mixture at such proportions that the melting point is as low as possible and that all the constituents crystallized simultaneously at this temperature called eutectic temperature from molten liquid solution[18]. In these figure all three phase can exist in equilibrium A, B, and melt.

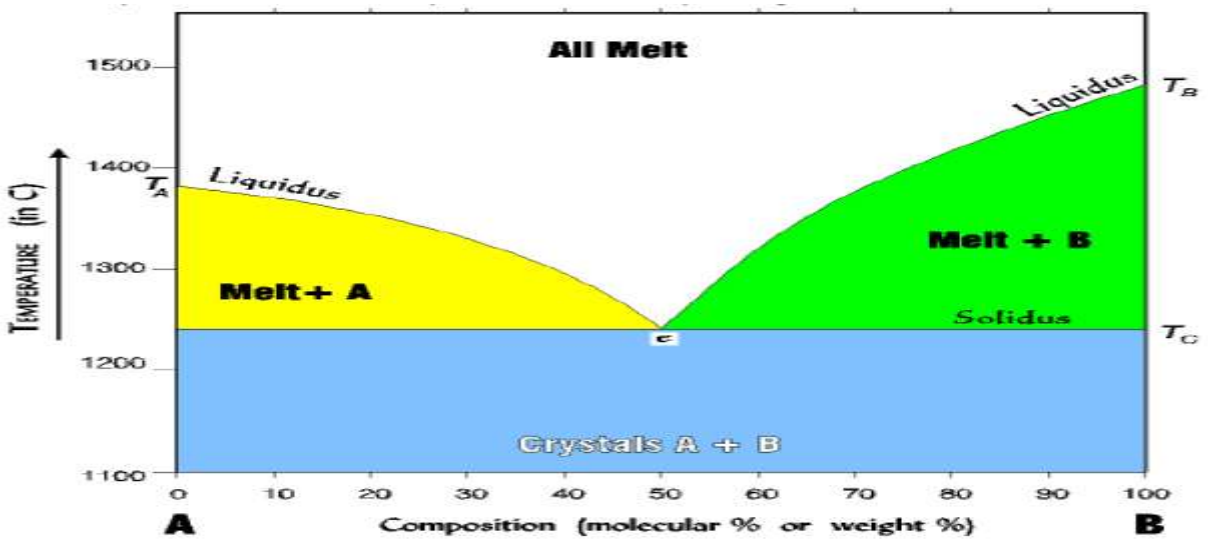


Figure 3: Organization of binary eutectic phase diagram

SOLID DISPERSION:

The solid dispersions may also be called as solid-state dispersions, as first introduced by Mayersohn and Gibaldi. The term "co-precipitates" has also been frequently used to refer to those preparations obtained by the solid dispersion methods. Hence the dissolution rate of a component from a surface is affected by the second component in a multiple component mixture; the selection of the carrier has an ultimate influence on the dissolution characteristics of the dispersed drug. Therefore, a water-soluble carrier results in a fast release of the drug from the matrix, and a poorly soluble or insoluble carrier leads to a slower release of the drug from the matrix[24]. The solid dispersion can be divided in following diagram.

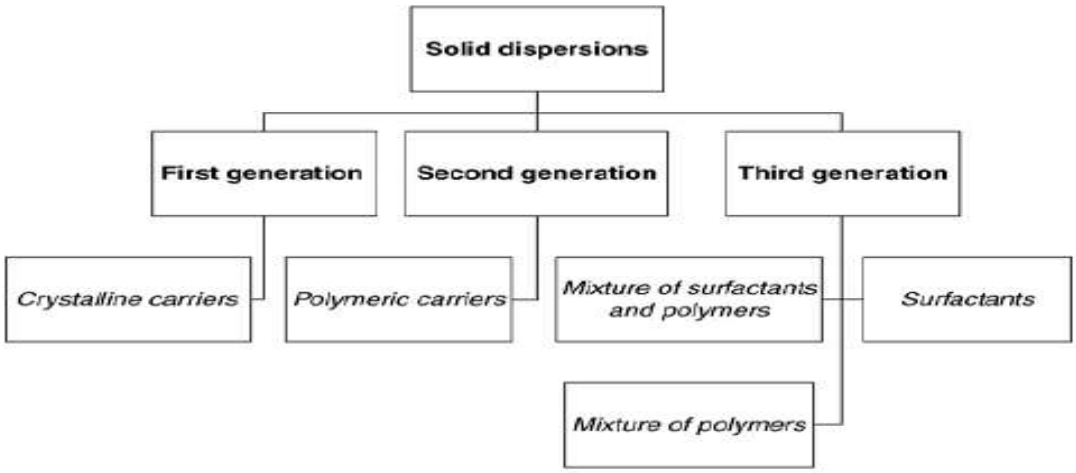


Figure 4: Show types of solid dispersion[25]

Table 2: Some solid dispersion of poorly water soluble drugs prepared by different methods

Drug	Polymer	Method	Solvent used
Fenofibrate	PEG6000, Poloxamer 407	Melt evaporation, Lyophillization	Chloroform
Glipizid	PEG6000, Mannitol PVPK30	Fusion(melt)method, Solvent evaporation method	Dichloromethane

Acyclovir	PEG6000,PVPK30	Solvent evaporation method	Methanol
Valdecoxib	PVP	Kneading	Water
Flurbiprofen	HPC	Solvent evaporation method	Ethanol
Efavirenz	PEG6000	Solvent evaporation method	Acetone (min.vol.)
Chlordiazepoxide	PVPK30, Mannitol	Co-precipitation method	Ethanol
Itraconazole	Eudragit	Melt method	-
Furosemide	Sodium starch glycolate	Kneading method	Water: ethanol
Tolbutamide	PEG 6000, β-cyclodextrin	Melt method	-

COMPLEXATION:

Complexation is the association between two or more molecules to form a nonbonded entity with a well-defined stoichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions.

STACHING COMPLEXATION:

Staching complexes are formed by the overlap of the planar regions of aromatic molecules. Nonpolar moieties tend to be squeezed out of water by the strong hydrogen bonding interactions of water. This causes some molecules to minimize the contact with water by aggregation of their hydrocarbon moieties. This aggregation is favored by large planar nonpolar regions in the molecule. Stached complexes can be homogeneous or mixed. The former is known as self-association and later as complexation. Some compounds that are known to form staching complexes are as follows.

Higuchi and Kristiansen proposed a model according to which the compounds capable of undergoing stacking can be classified into two classes (classes A and B) based on their structure[26]. The compounds in class A have higher affinity for compounds in class B than for those in class A and vice versa[27]. Nicotinamide, Anthracene, Pyrene, Methylene blue, Benzoic acid, Salicylic acid, Ferulic acid, Gentisic acid, Purine, Theobromine, Caffeine, and Naphthalene [28].

INCLUSION COMPLEXATION:

Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The major structural requirement for inclusion complexation is a snug fit of the guest into the cavity of host molecule. There are three naturally occurring Cyclodextrins are

i. α-Cyclodextrin,
ii. β-Cyclodextrin, and
iii. γ- Cyclodextrin.

The complexation with cyclodextrins is main aim to increase solubility[29]. Cyclodextrin inclusion is a molecular phenomenon in which usually only one guest molecule interacts with the cavity of a cyclodextrins molecule to become entrapped and form a stable association. The internal surface of cavity is hydrophobic and external is hydrophilic; this is due to the arrangement of hydroxyl group within the molecule. Complex formation of cyclosporine A[30] melarsoprol [31], Clofibrate[32], Rofecoxib[33], taxol[34] celecoxib[35], etc. with cyclodextrins improves the solubility of particular drugs. It was found that cyclodextrins increased the paclitaxel solubility by 950 fold[36]. Cyclodextrins is to enhance aqueous solubility of drugs through inclusion complexation.

SOLUBILIZATION BY SURFACTANTS:

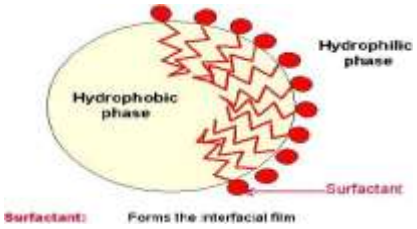
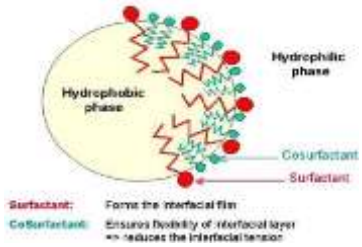
Surfactant is the important agent that can be used for enhancement of bioavailability of poorly hydrophobic drugs. Surfactants molecules having distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, and zwitterionic or nonionic[37.] When small a polar molecule are added they can accumulate in the hydrophobic core of the micelles. This process of solubilization is playing a vital role in industrial and biological processes. The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent[38].

MICROEMULSIONS:

Micro emulsions have been employed to increase the solubility of many drugs that are

practically insoluble in water, along with incorporation of proteins for oral, parenteral, as well as percutaneous/ transdermal use. The Hong-Mei Piao et.al increased the solubility of fexofenadine through microemulsion[62]. Liandong Hu et.al also increased the solubility of fenofibrate by formulating intranasal microemulsion[40-63]. There is basic difference between emulsion and microemulsion[39-40].

Table 3: Showing difference between emulsion and micro emulsion.

Emulsions (Macro emulsions)	**Micro emulsions**
 Emulsions	 Micro emulsions
Emulsions consist of roughly spherical droplets of one phase dispersed into the other.	They constantly evolve between various structures ranging from droplet like swollen micelles to bicontinuous structure.
Droplet diameter: 1 – 20 mm.	10 – 100 nm.
Most emulsions are opaque (white) because bulk of their droplets is greater than wavelength of light and most oils have higher refractive indices than water.	Micro emulsions are transparent or translucent as their droplet diameter are less than ¼ of the wavelength of light, they scatter little light.
Ordinary emulsion droplets, however small exist as individual entities until coalesance or Ostwald ripening occurs.	Micro emulsion droplet may disappear within a fraction of a second whilst another droplet forms spontaneously elsewhere in the system.
They may remain stable for long periods of time, will ultimately undergo phase separation on standing to attain a minimum in free energy. They are kinetically stable thermodynamically unstable.	More thermodynamically stable than micro emulsions and can have essentially infinite lifetime assuming no change in composition, temperature and pressure, and do not tend to separate.
They are lyophobic.	They are on the borderline between lyophobic and lyophilic colloids.
Require intense agitation for their formation.	Generally obtained by gentle mixing of ingredients.

1. CHEMICAL MODIFICATIONS:

The chemical modification include the changing pH of the system may be simplest and most

effective means of increasing aqueous solubility. Adjustment of micro-environmental pH to modify the ionization behavior is the simplest and most commonly used method to increase water solubility of ionizable compounds. As per pH-partition hypothesis and Handerson- Hesselbatch equation, ionization of a compound is dependent on the pH of media and pKa of drug. The change in the ionic milieu can also result to in situ salt formation. However, this salt formation is infeasible for unionized compounds [41]. Nonionizable hydrophobic substances can also have improved solubility by changing the dielectric constant of the solvent by the use of co-solvents rather than the pH of the solvent [42]. The formed salts may also converse to respective acid or base forms in gastrointestinal-tract. Under the proper conditions, the solubility of an ionizable drug can increase exponentially by adjusting the pH of the solution. By using chemical modification method's 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. Similar to the lack of effect of heat on the solubility of non-polar substances, there is little effect of pH on nonionizable substances the use of salt forms is a well-known technique to enhanced dissolution profiles[43]. Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs.

2. OTHER METHODS:

HYDROTROPHY:

Hydrotrophy is solubilization processes accrue by addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotropic agents like sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs [44]. Hydrotropes are used in detergent formulations to allow more concentrated formulations of surfactants[45].

NANOTECHNOLOGY:

Nanotechnology is important technique to be used for improve solubility of drugs that currently have poor solubility. Nanotechnology refers broadly to the study and use of materials and structures at the nan scale level of approximately 100 nanometers (nm) or less[46]. 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[47].

Table 4: Nanotechnology to improve solubility of hydrophobic drug

Nanoparticulate Technologies	Description
NAB (Nanoparticle Albumin-Bound technology)	Injectable suspension of biocompatible protein with Drug improves solubility/removes need for toxic solvents; e.g. paclitaxel-albumin nanoparticles, injectable suspension of biocompatible protein with drug improves.
CAP(Calcium Phosphate-based Nanoparticles)	For improved oral bioavailability of hormones proteins such as insulin; also as vaccine adjuvant.
Nanocrystal	Nanocrystal drug particles (<1,000 nm) produced by wet-milling and stabilized against agglomeration through surface adsorption of stabilizers; applied to NMEs e.g. aprepitant/reformulation of existing drugs e.g. Sirolimus.
IDD (Insoluble Drug Delivery)	Micro-nm particulate/droplet water-insoluble drug core stabilized by phospholipids; formulations are produced by high shear, cavitation's or impaction.

Nanoedge	Nanoedge technology: drug particle size reduction to Nano range by platforms including direct homogenization, micro precipitation, lipid emulsions and other dispersed-phase technology.

NANOCRYSTAL:

A nanocrystal is a crystalline material with dimensions measured in nanometers, a nanoparticle with a structure that is mostly crystalline. The nanocrystallization is defined as a way of diminishing drug particles to the size range of 1-1000 n.m. Nanocrystallization is thought to be a universal method that can be applied to any drug. There are two distinct methods used for producing nanocrystals 'bottom-up' and 'top-down' development. The top-down methods (i.e. Milling and High pressure homogenization) start milling down from macroscopic level, e.g. from a powder that is micron sized. In bottom-up methods (i.e. Precipitation and Cryo-vacuum method), Nano scale materials are chemically composed from atomic and molecular components[48].

COSOLVENCY:

Among them, use of co solvent (i.e., Co solvency) is one of the most popular approaches for improving the solubility of poorly aqueous soluble drugs in pharmaceutical liquid formulations[49]. Co solvents are the mixtures of miscible solvents often used to water which can dramatically change the solubility of poorly aqueous soluble drugs[50]. Weakly electrolytes and nonpolar molecules frequently have poor water solubility. Their solubility usually can be increased by the addition of water miscible solvent in which the drug has good solubility. This process is known as Co solvency, and the solvents used to increase solubility are known as co solvent. Co solvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly referred to as solvent blending[51]. Most co solvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen-bonding groups ensure water miscibility, while their hydrophobic hydrocarbon regions interfere with waters hydrogen bonding network, reducing the overall intermolecular attraction of water. By disrupting waters self-association, co solvents reduce waters ability to squeeze out nonpolar, hydrophobic compounds, thus increasing solubility[52]. Though Co-solvency has been highly utilized in the design of many different formulations, it has found its main use in parenteral dosage forms because of the irritating effects of most surfactants and the low toxicity of many co-solvents, and because of the relatively greater ability of co-solvents to solubilize nonpolar drugs. The most frequently used low toxicity co-solvents for parenteral use are propylene glycol, ethanol, glycerin, and polyethylene glycol[53-54].

CO-CRYSTALLISATION:

A co-crystal may be defined as a crystalline material that consists of two or more molecular species held together by non-covalent forces[55]. This is a new technique for the enhancement of drug solubility 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 crystals, 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[56]. Co-crystallisation between two active pharmaceutical ingredients has also been reported. This may require the use of sub therapeutic amounts of drug substances such as aspirin or acetaminophen[57]. Co-crystals are more stable, particularly as the co-crystallizing agents are solids at room temperature. Only three of the co-crystallizing agents are classified as generally recognized as safe (GRAS) it includes saccharin, Nicotinamide and acetic acid limiting the pharmaceutical applications[58]. Co-crystals can be prepared by evaporation of a heteromeric solution or by grinding the components together. Another technique for the preparation of co-crystals includes sublimation, growth from the melt, and slurry preparation[59]. The formation of molecular complexes and co-crystals is becoming increasingly important as an alternative to salt formation, particularly for neutral compounds or those having weakly ionizable groups.

USE OF SOLUBLE PRODRUG:

This recent concept is that uses of prodrug for the solubility enhancement of poorly soluble hydrophobic

drugs this process involve alteration of physico-chemical properties of the drug by bio-reversible chemical alteration. The most common prodrug strategy involves the incorporation of polar or ionizable moiety into the parent compound to improve aqueous solubility. The 'post hoc pro-drug approach' (prodrug of established drugs) has been successfully used to improve water solubility of corticosteroids, vitamins and benzodiazepines[60].

CONCULSION:

The solubility of the drug is the factor that controls the formulation of the drug as well as therapeutic efficacy of the drug, hence the most critical factor in the formulation development. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs and solubility is also the basic requirement for the formulation and development of different dosage form of different drugs. The various techniques described above alone or in combination can be used to enhance the solubility of the drug.

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