Current Pharma Research
ISSN-2230-7842
CODEN-CPRUE6
www.jcpronline.in/

Review Article

A Review on: Solubility Enhancement Techniques.

Anjali R. Kale*, Sujit Kakade, Ashok Bhosale

PDEA's Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Kharadi, Pune-14, Maharashtra, India.

Received 22 November 2019; received in revised form 14 January 2020; accepted 14 January 2020

***Corresponding author E-mail address:** *anjalikale002@gmail.com*

ABSTRACT

A drug administered within the form of solubility at once available for absorption and with efficiency absorbed than a similar quantity of drug administered during a pill or capsule kind. Solubility for oral bioavailability of poorly soluble drugs is most important. Solubility is one of the parameters to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Rate determining step of dissolution drug for oral absorption of poorly or less water soluble drug that affect of in vivo absorption of drug. Currently only 8% of new drug candidates have both high solubility and high permeability. Poorly water soluble has require high dose in oral administration before reach in plasma concentration. The major problem is low aqueous solubility similar with formulation development of new chemical entities. Any drug to be absorbed should be present within the form of associate solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of drugs has weakly acidic and basic with poor aqueous solubility. Because of solubility enhancement is necessary because many drugs solubility affect on bioavailability of drug. Now solubility is increase with the help of various techniques like Co-crystallization, co-solvency, hydrotrophy, pH adjustment, nanotechnology approaches and solid dispersion technique.

KEYWORD

Solubility, Solubility Enhancement, Dissolution, Bioavailability.

1. INTRODUCTION

Therapeutic effectiveness of a drug depends upon the bioavailability and solubility of drug molecules. Solubility is one of the important parameter to achieve bioavailability for pharmacological response to be shown. Now only 8% of new drug compound have both high solubility and permeability.[1] Solubility is defined as the concentration of the solute in a solution when equilibrium exists between the pure solute phase and the solution phase. At low concentrations, solubility is difficult to measure analytically, and at high concentrations, solubility is not an issue in the discovery process.[2] The drug solubility in saturated solution is a static property where as the drug dissolution rate is a dynamic property that relates more closely to the bioavailability rate.[3]

Table 1. The solubility of a drug is explains in various following terms which is depends on the amount of drug dissolved in solvent.

Descriptive terms	**Approximate volume of solvent in milliliters per gram of solute**
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to10,000
Insoluble	More than 10,000

A many method can be adapted to improve solubilization of poor water soluble drug and then to improve its bioavailability. The techniques generally employed for solubilization of drug includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc. Solubilization of less soluble drugs is a rapidly unexpected challenge in screening studies of new chemical molecule and in formulation design and formulation development.[4,5]

1.2. Need of Solubility[6]

Drug absorption in GIT can be limited by a variety of factors most particular part of poor aqueous solubility and poor membrane permeability of the drug molecule. When drug administered in orally it must firstly dissolve in gastric or intestinal fluids before it can permeate the membranes of the GIT to reach in blood. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include; enhancing of solubility and dissolution rate of poorly water soluble drugs. The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. As for BCS class II & IV drugs rate limiting step is drug release from the dosage form and solubility in gastric fluid

and not the, so increasing the solubility in turn increase the bioavailability for BCS class II & IV drugs [3].

Table 2. BCS classification system with examples of different drug.

BCS CLASS	FEATURES	EXAMPLE
BCS Class 1	High Solubility High Permeability	Beta-Blockers, Propanolol, Metoprolol
BCS C lass 2	Low Solubility High Permeability	NSAID's Ketoprofen, Antiepileptic Carazepine
BCS Class 3	High Solubility Low Permeability	B Blocker Atenolol,H2 antagonist Ranitide
BCS Class 4	Low Solubility Low Permeability	Diuretics Hydrochlorothiazide, frusemide

1.3. Process of Solubilization [7]

The process of solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvents and the solute molecule. When Solubilization process occur break down of solute bond occurs and holes can be seen as shown in step 1.

When solubilization process occur solid molecules break down because of breaking of inter molecular bonding shown in step 2. About freed solid molecule is integrated in the solvent shown in step 3.

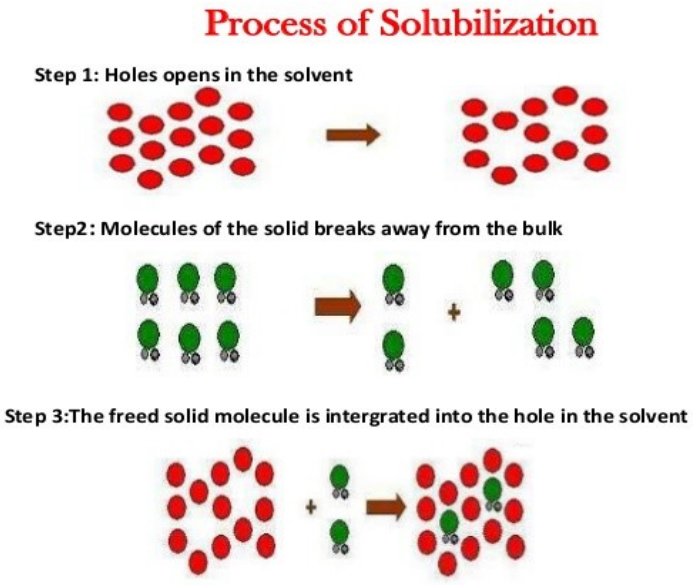

Fig. 1. The solid molecule is integrated into the hole in the solvent.

1.4. Factors Affecting Solubility

The solubility of drug depends on the physical form of the solid, the composition and nature of solvent and medium also temperature and pressure of system. [7]

1.4.1. Particle size

The particle size of the solid increases the solubility because as a particle size is small, the surface area to volume ratio increases. The larger surface area allows a greater interaction of drug with the solvent.

1.4.2. Temperature

Temperature will affect solubility. If the solution process absorbs energy then the solubility will be increased as the temperature is increased. If the solution process releases energy then the solubility will decrease with increasing temperature.[10] Generally, an increase in the temperature of the solution can increases the solubility of a solute. A few solid solutes are less soluble in warm temperature solutions. For all gases, solubility decreases as the temperature of the solution increases. [8]

1.4.3. Pressure

When pressure increases solubility can increase and pressure decreases can decrease the solubility. For gaseous solutes, when pressure increases solubility can increase and pressure decreases can decrease the solubility for solids and liquid solutes, changes in pressure have practically no effect on solubility.[8]

1.4.4. Nature of the solute and solvent

While only 1 gram of lead (II) chloride can be dissolved in 100 grams of water at room temperature and 200 grams of zinc chloride can be dissolved. The more difference in the solubilities of two substances is the result of differences in their nature. [9]

1.4.5. Molecular size

The large the molecule or high molecular weight the less soluble the substance. Larger molecules are more difficult to surrounding with solvent molecules. In the case of organic compounds the amount of carbon branching will increase the solubility of drug. Since more branching will reduce the size of the molecule and make it easier to solvate the molecules with solvent [10].

1.4.6. Polarity

Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract the negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction.[10]

1.4.7. Polymorphs

A solid has a rigid form and a definite shape. The shape or habit of a crystal of a given substance may vary but the angles between the faces are always constant. A crystal is made up of atoms, ions, or molecules in a regular geometric arrangement or lattice constantly repeated in three dimensions. This repeating pattern is known as the unit cell. The capacity for a substance to crystallize in more than one crystalline form is polymorphism.[11]

Techniques of solubility enhancement there are various techniques available to improve the solubility of poorly soluble drugs.

1.5. Methods for Solubility Enhancement

[1] Particle size reduction
[2] Co solvency
[3] Microemulsion
[4] Complexation
[5] Supercritical fluid
[6] Solid dispersion
[7] Hydrotrophy
[8] pH Adjustment
[9] Sonocrystalization
[10] Salt formation
[11] Cryogenic Techniques

1.5.1. Particle size reduction

The solubility of drug is related to drug particle size; as a particle becomes smaller, the surface area large. The larger surface area allows greater interaction with the solvent which causes an increase in solubility.[12]

Particle size reduction can be done by micronization and nanosuspension. Each technique utilizes more equipments for reduction of the particle size.

1.5.1.1. Micronization

The solubility of drug is often naturally related to drug particle size. By reducing the particle size, the surface area can increase, that improves the dissolution properties of the drug molecule. Conventional methods use for particle size reduction, such as comminution and spray drying, depend upon mechanical stress to separate the active compound. The micronization is used to increased surface area for dissolution. [13-14]

1.5.1.2. Nanosuspension

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilized by surfactants.[15] The advantages provide by nanosuspension is increased dissolution rate with larger surface area exposed, while absence of Ostwald ripening is due to the uniform and narrow particle size range obtained, which eliminates the concentration gradient factor.

1.5.1.3. Techniques for the production of nanosuspensions [15]

The suspension is forced under pressure through a valve that has nano aperture. This causes bubbles of water to form which collapses as they come out of valves. This mechanism cracks the particles. Three types of homogenizers are commonly used such as conventional homogenizers, sonicators, and high shear fluid processors.[16]

1.5.2. Co-solvent system

In this system poorly soluble drug solubility increase by addition of water miscible solvent in which the drug has good solubility known as cosolvents.[17] Mixtures of water and one or more

water miscible solvents used to create a solution with enhanced solubility for poorly soluble compounds are known as co-solvent. This technique is simple to produce and evaluate, hence historically this is one of the most widely used techniques. Examples of solvents used in co-solvent mixtures are PEG 300, propylene glycol. Co-solvent formulations of poorly soluble drugs can be administered orally and parenterally. 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 suitable to a co-solvent approach. Co-Solvents can increase the solubility of drug several thousand times compared to the aqueous solubility of the drug alone. Very high concentrations of poorly soluble drug compounds can be dissolved compared to other solubilization approaches. Co-solvents may be combined with other solubilization techniques and pH adjustment to further increase solubility of poorly soluble compounds. The use of cosolvents is a highly effective technique to enhance the solubility of poorly soluble drugs. [18–20] The most frequently used low toxicity co solvents for parenteral use are propylene glycol, glycerin, ethanol and polyethylene glycol.[21-24] Large solubilization capacity for poorly soluble drugs and their relatively low toxicity.[25-27] hence, Dimethyl sulfoxide (DMSO) and dimethyl acetoamide (DMA) have been widely used as cosolvents.

Table 2. List of Commonly Used Cosolvents in Formulation.

Ethanol	**Propylene Glycol**	**N-Methyl -2-Pyrrolidone**
Polyethylene Glycol	Glycerin	Butyrolactone
N, N-Dimethyl Acetamide	Dioxolanes	N-N-Dimethyl Formamide
Triglyme	Triacetin	N-Beta Hydroxyethyl Lactamide
Dimethyl Isosorbide	Diacetin	Benzyl Alcohol
1,2-Butylene Glycol	Glycerol Formal	Ethyl Lactate
Transcutol	Labrasol	Acetyl Triethyl Citrate

1.5.3. Microemulsion

The microemulsion term was first used by Jack H. Shulman in 1959. A microemulsion is a four component system. That is composed of external phase, internal phase, surfactant and co surfactant. When addition of surfactant, which is soluble in the internal phase unlike the cosurfactant, hence the results in the formation of an optically clear, isotropic, thermodynamically stable emulsion. It is termed as microemulsion because of the internal or dispersed phase is < 0.1 μ droplet diameter. [28-30]

1.5.4. Complexation

Complexation of drugs with cyclodextrins has been used to enhance aqueous solubility drug as well as drug stability. In pharmaceutical relevance of cyclodextrins contains 6, 7,8 dextrose

molecules (α, β, γ-cyclodextrin) bound in a 1,4configuration to form rings of various diameters. The ring has a hydrophilic exterior and lipophilic core in which appropriately sized organic molecules can form noncovalent inclusion complexes resulting in increased aqueous solubility and chemical stability.[31] When the low the aqueous solubility of the pure drug, then the greater the relative solubility enhancement obtained through cyclodextrin complexation. Pharmaceutical applications of cyclodextin in drug solubilization and stabilization [32], in vivo drug delivery [33], toxicological issues and safety evaluation and mechanisms of Cyclodextrins modifying drug release from polymeric drug delivery systems have been previously reviewed.

1.5.5. Super critical fluid extraction

The number of applications and technologies including supercritical fluids has also grown explosively. It has been known for more than a century that supercritical fluids (SCFs) can dissolve nonvolatile solvents, with the critical point of carbon dioxide, the most widely used supercritical fluid. It is safe, environmentally friendly, and economical. The low operating conditions such as temperature and pressure that make SCFs attractive for pharmaceutical research (Markku Rantakyla et al., 2004). A SCF exists as a single phase above its critical temperature (Tc) and critical pressure (Pc). SCFs having properties are intermediate between those of pure liquid and gas (i.e., liquid-like density, gas-like compressibility and viscosity and higher diffusivity than liquids) hence they useful to product processing. 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.[34,35] 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. Commonly used supercritical solvents include carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water. 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 micronization of drug particles within narrow ranges of particle size, often to sub-micron levels. Current SCF processes have demonstrated the ability to create nanosuspensions of particles 5-2,000nm in diameter. Several pharmaceutical companies, such as Nektar Therapeutics and Lavipharm, are specializing in particle engineering via SCF technologies for particle size reduction and solubility enhancement.[36,37]Several methods of SCF processing have been developed to address individual aspects of these shortcomings, such as precipitation with compressed antisolvents process (PCA), Rapid Expansion of Supercritical Solutions, Gas Antisolvent Recrystallization, Precipitation with Compressed Fluid Antisolvent, Impregnation or infusion of polymers with bioactive materials, Solution enhanced Dispersion by Supercritical Fluid, solution enhanced dispersion by SCF (SEDS), supercritical antisolvents processes (SAS) and aerosol supercritical extraction system (ASES).[38,39]

1.5.6. Solid solutions/dispersions

Solid dispersion is defined as a dispersion of one or more active ingredients in an inert carrier at solid state. It was initially introduced to overcome the low bioavailability of lipophilic drugs by forming of eutectic mixtures of drugs with water-soluble carriers. Solid dispersion defined as the dispersion of one or more active ingredients in an inert carrier matrix in solid-state prepared by melting (fusion), solvent or melting-solvent method. The solubility of Celecoxib, Halofantrine, Ritonavir can be improved by solid dispersion using suitable hydrophilic carriers.[40-42]

1.5.6.1. Method of solid dispersions

1.5.6.1.1. Hot melt method (fusion method)

In this method, the physical mixture of a drug and a water-soluble carrier was heated upto it melted. The melted mixture was cooled then solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed, pulverized, and sieved, which can be use compressed into tablets with the help of tableting agents. The melting point of a binary system is dependent upon its composition, i.e., the selection of the carrier and the weight fraction of the drug in the system. As important for the formation of solid dispersion by the hot melt method is the miscibility of the drug and the carrier in the molten form. Another important requisite is the thermo stability of the drug and carrier.

1.5.6.1.2. Solvent Evaporation Method

Tachibana and Nakumara were the first scientist which was to dissolve both the drug and the carrier in a common solvent .then evaporate the solvent under pressure to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic β-carotene in the highly water soluble carrier polyvinyl pyrrolidone. The main advantage of the solvent method is the thermal decomposition of drugs or carriers. Which can be prevented because of the low temperature required for the evaporation of organic solvents? However, some disadvantages related with this method are the higher cost of preparation and the difficulty in completely removing liquid solvent, the possible adverse effect of the supposedly negligible amount of the solvent on the chemical stability of the drug, the selection of a common volatile solvent, and the difficulty of reproducing crystal forms.

1.5.6.1.3. Hot melt extrusion

Hot melt extrusion is essentially the similar as the fusion method except, that immediately mixing of the components is induced by the extruder. As like in the traditional fusion process, miscibility of drug and matrix can be a problem. High shear forces resulting in high local temperature in the extruder is a problem for heat sensitive materials. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can adapted to the next processing step without grinding. Solid dispersion can be characterized with several analytical methods. FT-IR Spectroscopy, scanning electron microscopy (SEM), X-ray diffraction, dissolution rate determination and thermal analysis methods like thermo-microscopic method, differential thermal analysis (DTA), and differential scanning colorimetry (DSC) can be employed for solid dispersion evaluation.[42]

1.5.6.1.4. Co-evaporate System / Co-precipitation

Weak basic drugs like Prochlorperazine Maleate contain good solubility in acidic pH but in alkaline pH solubility is can reduced and when a conventional formulation containing weak base is given orally precipitation of poorly soluble free base occurs within formulation in intestinal fluid. Precipitated drug is no longer capable of release from formulation leading to decrease in bioavailability of drug. This problem can be solved by use of co-evaporate system which incorporates a carrier with solubilizing effect in alkaline intestinal fluid which may operate in the microenvironment, immediately surrounding the drug particle and polymers for controlling the dissolution rate to formulate dosage forms ensuring maximum bioavailability with controlled release of weak base.[40]

1.5.6.1.5. Inclusion Complexes

Cyclodextrins are a group of cyclic oligosaccharides obtained from enzymatic degradation of starch. The three major cyclodextrins α, ß, and γ-CD are composed of six, seven, and eight D-(+) -glucopyranose units. These agents have a torus structure with primary and secondary hydroxyl groups orientated outwards. Consequently, cyclodextrins have a hydrophilic exterior and also hydrophobic internal cavity. CD and their derivatives have been employed as complexing agents to increase water solubility, dissolution rate and bioavailability of lipophilic drugs for oral or parenteral delivery.[40]

1.5.6.1.6. Supercritical fluid method

A supercritical fluid (SCF) procedure has been allows the micronization of drug particles inside sub-micron levels. Supercritical fluids are the fluids whose temperature and pressure are superior than critical temperature (Tc) and critical pressure (Tp). At near-critical temperature, SCFs are highly compressible as well as allowing reasonable changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely decide its solvent power. Once the drug particles are solubilized within SCF, they may be recrystallized at greatly reduced particle size. Carbon dioxide and water are the most usually used supercritical fluids. The SCF process can create nanoparticulate suspensions of particles 5–2,000 nm in diameter. E.g. enhancing water solubility of itraconazole with water soluble polymer HPMC by using supercritical fluid processing.[41,42]

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, often prepared by the melting method, solvent method, or fusion solvent-method. Novel additional preparation techniques have included rapid precipitation by freeze drying and by means of supercritical fluids and spray drying, often in the presence of amorphous hydrophilic polymers and also using methods such as melt extrusion. The most commonly used hydrophilic carriers for solid dispersions include polyvinyl pyrrolidone, polyethylene glycols, and plasdone-S630. Many times surfactants may also use in the formation of solid dispersion. Surfactants like Tween-80, docusate sodium, Myrj-52, Pluronic-F68 poloxamer and sodium lauryl Sulphate used.

1.5.7. Hydrotrophy

Hydrotrophy is a solubilization process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. Most of the alkali metal salts of various organic acid contains solute molecule. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to be "salt in" the solute and those salts that decrease solubility "salt out" the solute. More amount salts with large anions or cations that are themselves very soluble in water result in "salting in" of non-electrolytes called "hydrotropic salts" a phenomenon known as "hydrotropism". Hydrotropic solutions do not show colloidal properties. It involves a weak interaction between the hydrotropic agent and 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 hydrotrophic agents like sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs.[44-47]

1.5.7.1. Advantages of Hydrotropic Solubilization Technique

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. It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.

The hydrotropes are 6-known to self-assemble in solution.[48] The classification of hydrotropes on the basis of molecular structure is difficult, since a wide variety of compounds have been reported to exhibit hydrotropic behaviour. Specific examples may include ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, a- and b- naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate) and deacylated oxidibenzene.[49] The aromatic hydrotropes with anionic head groups are mostly studied compounds. They are large in number because of isomerism and their effective hydrotrope action may be due to the availability of interactive orbitals. Hydrotropes with cationic hydrophilic group are rare, e.g. salts of aromatic amines, such as procaine hydrochloride. Besides enhancing the solubilization of compounds in water, they are known to exhibit influences on surfactant aggregation leading to micelle formation, phase manifestation of multi component systems with reference to nano dispersions and conductance percolation, clouding of surfactants and polymers, etc. Other techniques that enhance the solubility of poorly water soluble drugs include salt formation, change in dielectric constant of solvent, Chemical modification of the drug, use of hydrates or solvates, use of Soluble prodrug, Application of ultrasonic waves, spherical crystallization.[50]

1.5.8. pH adjustment

Poorly water soluble drugs with parts of the molecule that can be protonated or deprotonated and may be potentially be dissolved in water by applying a pH in change. For oral and parenteral administration the pH adjustment principle can be used. Intravenous administration he poorly soluble drug may be precipitate because blood is a strong buffer with pH between 7.2 – 7.4. To

assess the suitability of the approach, the buffer capacity and tolerability of the selected pH are important to consider. In the stomach the pH is around 1 to 2 and in the duodenum the pH is between 5-7.5, so upon oral administration the degree of solubility is also likely be influenced as the drug passes through the intestines. Ionizable compounds that are stable and soluble after pH adjustment are best suited. The types of compound may be acids or bases or zwitterionic. It can also be used to crystalline and also lipophilic poorly soluble compounds.[51-54] Solubilized excipients that increase environmental pH within a dosage form, such as a tablet or capsule, to a range higher than pKa of weakly-acidic drugs increases the solubility of that drug, those excipients which act as alkalizing agents may increase the solubility of weakly basic drugs.[55]

The solubility of the poorly soluble drug is increased compared to water separately, so if compounds can permeate through the epithelium orally, the fraction of orally absorbed drug may be increased. pH adjustment is also frequently combined with co-solvents to further increase the solubility of the poorly soluble drug. If the precipitation upon dilution is fine or amorphous, bioavailability can be increased due to an increased concentration gradient and enhanced surface area for dissolution. In situations where the drug precipitates into poorly soluble particles that require dissolution and do not rapidly redissolve, bioavailability may not be sufficiently increased. This approach is used frequently in Survey as pre-clinically pH adjustment is a good technique to assess the efficacy of poorly soluble drugs due to its universality and relative simplicity. However, if precipitation of the poorly soluble drug occurs uncontrollably after contact with a pH at which the drug is much less soluble (oral as well as parenteral), the interpretation of the results may be misleading.

1.5.8.1. Advantages

[1] It Simple to formulate and analyse.

[2] It Simple to produce and fast track.

[3] It uses small quantities of compound, amenable to high throughput evaluations.

1.5.8.2. Disadvantages

[1] Risk for precipitation upon dilution with aqueous media having a pH at which the compound is less soluble.

[2] Intravenously this may lead to emboli, orally it may cause variability.

[3] Tolerability and toxicity (local and systemic) related with the use of a non physiological pH and extreme pHs.

As with all solubilized and dissolved systems, a dissolved drug in an aqueous environment is frequently less stable chemically compared to formulations crystalline solid. The selected pH may accelerate hydrolysis or catalyze other degradation mechanisms.

1.5.9. Sonocrystallization [56]

Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size. The novel approach for particle size reduction on the basis of crystallization by using ultrasound is Sonocrystallisation. Sonocrystallisation utilizes ultrasound power characterized by a frequency range of 20-100 kHz for inducing crystallization. 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.

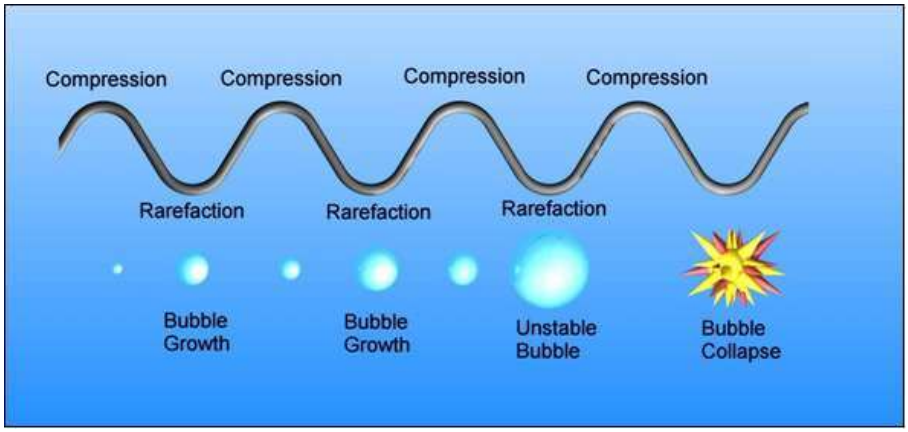

Fig. 2. Process of sonocrystallisation[57]

1.5.10. Salt formation

Salt formation of poorly soluble drug candidates (weak acids and bases) has been a method for many decades to reinforce solubility. It is associate successful technique in channel and other liquid formulations, further as in solid dose sorts of some three hundred new chemical entities approved by the federal agency throughout the twelve years from 1995 to 2006 for selling, one hundred twenty were in salt forms. In count, out of the 101 approved salts of basic medication, 54 salts were prepared with acid, representing the coordination compound was the predominant salt form the binary compound solubility of associate acidic or basic drug as a perform of pH scale dictates whether or not the compound can type appropriate salts. The pH-solubility interrelationships also dictate what counter ions would be necessary to form salts, how easily the salts may dissociate into their free acid or base forms, what their dissolution behavior would be under different GI pH conditions, and whether solubility and dissolution rate of salts would be influenced by common ion. Several reviews have made public general strategies and concerns for salt choice. For the salt formation drug should have ionizable teams that will assist salt formation. The criteria used to select counter ion is as follows: a) There should be least difference of 2-3 pKa units between the drug and the counter ion. b) Counter ion should decrease crystal lattice forces. c) It must be FDA approved or should have sufficient toxicological data to support the selection of the counter ion. d) This technique has tremendous capability to enhance dissolution rate but it is grasped with disadvantages like approval of salts is a tedious task and also not useful for neutral molecules.[58]

1.5.11. Cryogenic Techniques

Cryogenic techniques are developed to enhance the dissolution rate of medicine by making nanostructured amorphous drug particles with high degree of porosity at very cold conditions. A cryogenic invention is outlined by the kind of injection device (capillary, rotary, pneumatic, unhearable nozzle), location of nozzle (above or under the liquid level) and also the composition

of cryogenic liquid (hydrofluoroalkanes, N2, Ar, O2, organic solvents). After cryogenic process, dry powder is obtained by various drying processes like spray freeze drying,[59] atmospheric freeze drying, vacuum freeze drying and lyophilization. [60]

Spray freezing onto cryogenic fluids: Briggs and Maxwell[61] invented the process of spray freezing onto cryogenic fluid. 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. Sonication probe can be placed in the stirred refrigerant to enhance the dispersion of aqueous solution.

Spray freezing into cryogenic fluids (SFL): The SFL particle engineering technology has been used to produce amorphous nanostructured aggregates of drug powder with high area and good wettability.[62] It incorporates direct liquid – liquid impingement between the automized feed solution and cyogenic liquid to provide more intense atomization into microdroplets and consequently significantly faster freezing rates. The frozen particles are then lyophilized to obtain dry and free-flowing micronized powders. Hua et al[63] produced the rapid dissolving high potency Danazol powders by using Spray Freezing into liquid process.

Spray chilling into vapor over liquid (SFV/L): freezing of medicine solution in cryogenic fluid vapours and subsequent removal of frozen solvent produces fine drug particles with high wettability.[64] during SFV/L the atomized droplets generally begin to freeze in the vapor part before they contact the cryogenic liquid. As the solvent freezes, the drug becomes supersaturated in the unfrozen regions of the atomized droplet, so fine drug particles may nucleate and grow.

Ultra-Rapid chilling (URF): Ultra-rapid chilling could be a novel refrigerant technology that creates nanostructured drug particles with greatly enhanced area and desired surface morphology by mistreatment solid refrigerant substances. Application of medicine answer to the solid surface of refrigerant substrate resulting in fast chilling and subsequent freezing for removal of solvent forms micronized drug powder with improved solubility. Ultra-speedy chilling hinders the phase separation and therefore the crystallization of the pharmaceutical ingredients resulting in intimately mixed amorphous drug-carrier solid dispersions and solid solutions. This technique has been investigated for the solubility enhancement of repaglinide.

Floating Granules Patel Rajanikant et al.[64] utilized a novel approach for dissolution enhancement of ibuprofen by preparing floating formulation.

Ibuprofen, a weekly acidic, non-steroidal anti inflammatory drug having high permeability through stomach because it remain 99.9 % unionize in stomach (pKa of Ibuprofen - 4.43, pH of gastric fluid - 1.2). Ibuprofen mostly permeable through stomach however thanks to its solubility limitation it can’t enter in to systemic circulation and gastric emptying time is 30 min to 2 units of time. After this time ibuprofen goes in to small intestine where it is solubilized but can’t permeate through its membrane (Ibuprofen having pH depended solubility and permeability). It was logically set to style such formulations that retain in stomach for over two hrs as a result of drug wasn't fully soluble inside two hrs thence to dissolve completely in abdomen region; this can be achieved by making floating dosage form.

Floating ibuprofen granules were prepared by fusion method. 200 mg ibuprofen divided in to 50 mg and 150 mg, 350 mg gelucire 44/14 melted and 50 mg ibuprofen-fen
added, disperse with glass road for uniform distribution of drug in to molted carrier, remaining 150 mg ibuprofen added in to molted Gelucire 44/14, this whole dispersion added in to molted gelucire 43/01. In optimized formulation, Granules stay floated for 3 hrs., gave 100% drug release in 150 minutes in stomach region where it stay in 99.9% unionize form and absorbed to systemic circulation.

2. CONCLUSION

By this article we conclude that, solubility of the drug is the most important factor that controls the formulation of the drug and therapeutic efficacy of the drug. 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 many techniques described above separately or in combination can be used to enhance the solubility of the drug. Solubility can be enhanced by many techniques and many numbers of folds increase in solubility. Because, solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. It is now possible that to increase the solubility of poorly soluble drugs with the help of various techniques as mentioned above.

7. REFERENCES

1. Rani, T. N., Muzeeb, Y. I., Rani, P. S., & Pradesh, A. (2013). Solubility Enhancement of Poorly Soluble Drug Ezetimibe by Solid Dispersion Technique. *J. Adv. Pharm. Educ. Res*, 4, 75-81.
2. Johnson, S. R., & Zheng, W. (2006). Recent progress in the computational prediction of aqueous solubility and absorption. *The AAPS journal*, 8(1), E27-E40.
3. Limbachiya, M. I., Agarwal, M., Sapariya, A., & Soni, S. (2011). Solubility enhancement techniques for poorly soluble drugs: A review. *Int J Pharm Sci Rev Res*, 4, 71-86.
4. Bittner, B., & Mountfield, R. J. (2002). Formulations and related activities for the oral administration of poorly water-soluble compounds in early discovery animal studies: an overview of frequently applied approaches. Part 1. *Drugs made in Germany*, 45(1), 18-24.
5. Bittner, B., & Mountfield, R. J. (2002). Intravenous administration of poorly soluble new drug entities in early drug discovery: the potential impact of formulation on pharmacokinetic parameters. *Current opinion in drug discovery & development*, 5(1), 59-71.
6. Jain, A., Ran, Y., & Yalkowsky, S. H. (2004). Effect of pH-sodium lauryl sulfate combination on solubilization of PG-300995 (an anti-HIV agent): a technical note. *AAPS PharmSciTech*, 5(3), 65-67.

7. Patel, J. N., Rathod, D. M., Patel, N. A., & Modasiya, M. K. (2012). Techniques to improve the solubility of poorly soluble drugs. *International Journal of Pharmacy & Life Sciences*, 3(2).

8. Thakur, A. K., Nirmala, N., & Harikumar, S. L. (2013). Various techniques enhancing bioavailability of poorly water soluble drugs. *Journal of Drug Delivery and Therapeutics*, 3(2).

9. Patel, J. N., Rathod, D. M., Patel, N. A., & Modasiya, M. K. (2012). Techniques to improve the solubility of poorly soluble drugs. *International Journal of Pharmacy & Life Sciences*, 3(2).

10. Ain, S., Ain, Q., & Parveen, S. (2009). An overview on various approaches used for solubilization of poorly soluble drugs. *Pharm. Res*, 2, 84-104.

11. Singhal, D., & Curatolo, W. (2004). Drug polymorphism and dosage form design: a practical perspective. *Advanced drug delivery reviews*, 56(3), 335-347.

12. Kumar, S., & Singh, P. (2016). Various techniques for solubility enhancement: An overview. *The Pharma Innovation*, 5(1, Part A), 23.

13. Chaumeil, J. C. (1998). Micronization: a method of improving the bioavailability of poorly soluble drugs. *Methods and findings in experimental and clinical pharmacology,* 20(3), 211-216.

14. Blagden, N., de Matas, M., Gavan, P. T., & York, P. (2007). Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. *Advanced drug delivery reviews*, 59(7), 617-630.

15. Kirupakar, B. R. (2009). Nanosuspension drug delivery: technology and application. *Express Pharma Pulse*, 16.

16. Gowthamarajan, K., & Singh, S. K. (2010). Dissolution testing for poorly soluble drugs: a continuing perspective. *Dissolution Technologies*, 17(3), 24-32.

17. Strickley, R. G. (2004). Solubilizing excipients in oral and injectable formulations. *Pharmaceutical research*, 21(2), 201-230.

18. Millard, J. W., Alvarez-Nunez, F. A., & Yalkowsky, S. H. (2002). Solubilization by cosolvents: Establishing useful constants for the log–linear model. *International Journal of Pharmaceutics*, 245(1-2), 153-166.

19. Vemula, V. R., Lagishetty, V., & Lingala, S. (2010). Solubility enhancement techniques. *International journal of pharmaceutical sciences review and research*, 5(1), 41-51.

20. Zhao, L., Li, P., & Yalkowsky, S. H. (1999). Solubilization of fluasterone. *Journal of pharmaceutical sciences*, 88(10), 967-969.

21. Yalkowsky, S. H., & Rubino, J. T. (1985). Solubilization by cosolvents I: organic solutes in propylene glycol–water mixtures. *Journal of pharmaceutical sciences*, 74(4), 416-421.

22. Pan, L., Ho, Q., Tsutsui, K., & Takahashi, L. (2001). Comparison of chromatographic and spectroscopic methods used to rank compounds for aqueous solubility. *Journal of Pharmaceutical sciences,* 90(4), 521-529.

23. Nema, S., Washkuhn, R. J., & Brendel, R. J. (1997). Excipients and their use in injectable products. *PDA Journal of Pharmaceutical Science and Technology*, 51(4), 166-171.

24. Rubino, J. T., & Yalkowsky, S. H. (1987). Cosolvency and deviations from log-linear solubilization. *Pharmaceutical research*, 4(3), 231-236.

25. Rubino, J. T., & Yalkowsky, S. H. (1987). Cosolvency and deviations from log-linear solubilization. *Pharmaceutical research*, 4(3), 231-236.

26. Fernandes, P. B., & Seethala, R. (Eds.). (2001). Handbook of Drug Screening. Marcel Dekker.

27. Seedher, N., & Bhatia, S. (2003). Solubility enhancement of Cox-2 inhibitors using various solvent systems. *AAPS Pharmscitech*, 4(3), 36-44.

28. Tenjarla, S. (1999). Microemulsions: an overview and pharmaceutical applications. Critical Reviews™ in Therapeutic Drug Carrier Systems, 16(5).

29. Lieberman, H. A., Rieger, M. M., & Banker, G. S. (1996). Pharmaceutical dosage forms: disperse system. Marcel Dekker Inc., New York, hal, 57, 157-158.

30. Kovarik, J. M., Mueller, E. A., Kutz, K., Van Bree, J. B., & Tetzloff, W. (1994). Reduced inter-and intraindividual variability in cyclosporine pharmacokinetics from a microemulsion formulation. *Journal of pharmaceutical sciences*, 83(3), 444-446.

31. Loftsson, T., & Brewster, M. E. (1996). Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization. *Journal of pharmaceutical sciences*, 85(10), 1017-1025.

32. Challa, R., Ahuja, A., Ali, J., & Khar, R. K. (2005). Cyclodextrins in drug delivery: an updated review. *Aaps Pharmscitech*, 6(2), E329-E357.

33. Rajewski, R. A., & Stella, V. J. (1996). Pharmaceutical applications of cyclodextrins. 2. In vivo drug delivery. *Journal of pharmaceutical sciences*, 85(11), 1142-1169.

34. Phillips, E. M., & Stella, V. J. (1993). Rapid expansion from supercritical solutions: application to pharmaceutical processes. *International journal of pharmaceutics*, 94(1-3), 1-10.

35. Subramaniam, B., Rajewski, R. A., & Snavely, K. (1997). Pharmaceutical processing with supercritical carbon dioxide. *Journal of pharmaceutical sciences*, 86(8), 885-890.

36. Manna, L., Banchero, M., Sola, D., Ferri, A., Ronchetti, S., & Sicardi, S. (2007). Impregnation of PVP microparticles with ketoprofen in the presence of supercritical CO2. *The Journal of supercritical fluids*, 42(3), 378-384.

37. Martin, T. M., Bandi, N., Shulz, R., Roberts, C. B., & Kompella, U. B. (2002). Preparation of budesonide and budesonide-PLA microparticles using supercritical fluid precipitation technology. *AAPS PharmSciTech*, 3(3), 16-26.

38. Won, D. H., Kim, M. S., Lee, S., Park, J. S., & Hwang, S. J. (2005). Improved physicochemical characteristics of felodipine solid dispersion particles by supercritical anti-solvent precipitation process. I*nternational journal of pharmaceutics*, 301(1-2), 199-208.

39. Dohrn, R., Bertakis, E., Behrend, O., Voutsas, E., & Tassios, D. (2007). Melting point depression by using supercritical CO2 for a novel melt dispersion micronization process. *Journal of Molecular Liquids*, 131, 53-59.

40. Thorat, Y. S., Gonjari, I. D., & Hosmani, A. H. (2011). Solubility enhancement techniques: a review on conventional and novel approaches. *International journal of pharmaceutical sciences and research*, 2(10), 2501.

41. Zaheer, A., Naveen, M., Santosh, M. K., & Imran, K. (2011). Solubility enhancement of poorly water soluble drugs: A review. *IJPT*, 3(1), 807-82.

42. Wairkar, S. M., & Gaud, R. S. (2013). Solid dispersions: Solubility enhancement technique for poorly soluble drugs. *International Journal of Research in Pharmaceutical and Biomedical Sciences*, 4(3), 847.

43. Gaikwad, S. S., Mhalaskar, R. S., Mahale, Y. D., & Jain, N. P. (2014). Review on: solubility enhancement of poorly water soluble drug. *Indo Am J Pharm Res*, 4, 5530-5541.

44. Maliwal, D., Jain, A., Maheshwari, R. K., & Patidar, V. (2008). Simultaneous spectrophotometric estimation of metronidazole and norfloxacin in combined tablet formulations using hydrotropy. *Research Journal of Pharmacy and Technology*, 1(4), 357-361.

45. Saleh, A. M., & Daabis, N. A. (1974). Study of the interaction of menadione with hydrotropic salts. *Die Pharmazie*, 29(8), 525.

46. Rasool, A. A., Hussain, A. A., & Dittert, L. W. (1991). Solubility enhancement of some water-insoluble drugs in the presence of nicotinamide and related compounds. *Journal of pharmaceutical sciences*, 80(4), 387-393.

47. Badwan, A. A., El-Khordagui, L. K., Saleh, A. M., & Khalil, S. A. (1982). The solubility of benzodiazepines in sodium salicylate solution and a proposed mechanism for hydrotropic solubilization. *International journal of Pharmaceutics*, 13(1), 67-74.

48. Friberg, S. E., Lochhead, R. V., Blute, I., &Wertheim, T. (2004). Hydrotropes-performance chemicals. *Journal of dispersion science and technology*, 25(3), 243-251.

49. Roy, B. K., & Moulik, S. P. (2002). Functions of hydrotropes (sodium salicylate, proline, pyrogallol, resorcinol and urea) in solution with special reference to amphiphile behaviours. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 203(1-3), 155-166.

50. Patil, S. V., & Sahoo, S. K. (2010). Pharmaceutical overview of spherical crystallization. *Der Pharmacia Lettre*, 2(1), 421-426.

51. Vemula, Varun Raj, Venkateshwarlu Lagishetty, and Srikanth Lingala. "Solubility enhancement techniques." *International journal of pharmaceutical sciences review and research*, 5.1 (2010): 41-51.

52. Chaudhary, A., Nagaich, U., Gulati, N., Sharma, V. K., Khosa, R. L., & Partapur, M. U. (2012). Enhancement of solubilization and bioavailability of poorly soluble drugs by

physical and chemical modifications: A recent review. *J Adv Pharm Educ Res*, 2(1), 32-67.

53. McMorland, G. H., Douglas, M. J., Jeffery, W. K., Ross, P. L., Axelson, J. E., Kim, J. H., Robertson, K. (1986). Effect of pH-adjustment of bupivacaine on onset and duration of epidural analgesia in parturients. *Canadian Anaesthetists' Society Journal*, 33(5), 537-541.

54. Jain, A., Ran, Y., & Yalkowsky, S. H. (2004). Effect of pH-sodium lauryl sulfate combination on solubilization of PG-300995 (an anti-HIV agent): a technical note. *AAPS PharmSciTech*, 5(3), 65-67.

55. Kumar, S., & Singh, P. (2016). Various techniques for solubility enhancement: An overview. *The Pharma Innovation*, 5(1, Part A), 23.

56. Varshney, H. M., & Chatterjee, A. (2012). Solubility enhancement of poorly hydrophilic drugs by using different newer techniques: A Review. *International Journal of Therapeutic Applications*, 6(8), 13.

57. Thorat, Y. S., Gonjari, I. D., & Hosmani, A. H. (2011). Solubility enhancement techniques: a review on conventional and novel approaches. *International journal of pharmaceutical sciences and research*, 2(10), 2501.

58. Mumenthaler, M., & Leuenberger, H. (1991). Atmospheric spray-freeze drying: a suitable alternative in freeze-drying technology. *International Journal of Pharmaceutics*, 72(2), 97-110.

59. Briggs, A., & Maxwell, T. (1973). U.S. Patent No. 3,721,725. Washington, DC: U.S. Patent and Trademark Office.

60. Rogers, T. L., Hu, J., Yu, Z., Johnston, K. P., & Williams III, R. O. (2002). A novel particle engineering technology: spray-freezing into liquid. *International Journal of pharmaceutics*, *242*(1-2), 93-100.

61. Buxton, I. R., & Peach, J. M. (1984). *U.S. Patent No. 4,470,202*. Washington, DC: U.S. Patent and Trademark Office.

62. Hu, J., Johnston, K. P., & Williams III, R. O. (2004). Rapid dissolving high potency danazol powders produced by spray freezing into liquid process. *International journal of pharmaceutics*, *271*(1-2), 145-154.

63. Purvis, T., Mattucci, M. E., Crisp, M. T., Johnston, K. P., & Williams, R. O. (2007). Rapidly dissolving repaglinide powders produced by the ultra-rapid freezing process. *AAPS PharmSciTech*, *8*(3), E52-E60.

64. Rajanikant, P., Nirav, P., Patel, N. M., & Patel, M. M. (2010). A novel approach for dissolution enhancement of Ibuprofen by preparing floating granules. *International Journal of Research in Pharmaceutical Sciences*, *1*(1).