World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

NOVEL APPROACHES FOR SOLUBILITY ENHANCEMENT OF POORLY SOLUBLE DRUGS

Roobal Chaudhary* and Gagandeep Kaur

Assistant Professor, University Institute of Pharma Sciences, Chandigarh University, Gharuan, Mohali, Punjab.

***Corresponding Author: Roobal Chaudhary**

Assistant Professor, University Institute of Pharma Sciences, Chandigarh University, Gharuan, Mohali, Punjab

Article Received on 13/04/2020 **Article Revised on 04/05/2020** **Article Accepted on 25/05/2020**

ABSTRACT

Solubility is one of the most critical criteria for achieving optimal concentration of the drug in systemic circulation to exert therapeutic effect. Solubility can be defined as the solute dissolving phenomenon to give a homogenous system. An effective formulation depends on how effectively drug is made available at the place of action. Drugs having high aqueous solubility get absorbed through GIT membrane and reaches in systemic circulation easily. Poor aqueous solubility is the main problem facing the development of new API formulations and generic production. The solubility and dissolution rate of poorly soluble drugs must therefore be increased, because these drugs are weak in absorption and less bioavailable. This review is intended to with discuss thoroughly different techniques employed to enhance the aqueous solubility along appropriate examples of drugs whose solubility is enhanced by these techniques. There are number of solubility enhancement techniques include micronization, nanonization, super critical fluid method, spray freezing into liquids, hydrotropy method, solid dispersion, salt formation, co-solvency, addition of solubilizing agents, complexation and pH adjustment etc. Selection of the method for enhancing the solubility depends on the drug properties, the site of absorption and the features of the appropriate dosage type. The purpose of this review article is to describe BCS classification system, various solubility enhancement techniques of poorly soluble drugs with increased bioavailability for successful absorption and also tried to focus on the factors affecting process of solubilization.

KEYWORDS: bioavailability, micronization, nanonization, hydrotropy, BCS classification.

INTRODUCTION

About 90% drugs are administered orally as this route is easily accepted by patients and due to ease of production. Once delivered by mouth, the first necessary step is dissolution of drug in the body fluids, before it can permeate the GI tract membranes to enter systemic circulation. Since solubility is an essential factor in drug absorption, its bioavailability plays a key role. Drug solubility is the overall concentration of the substance dissolved in specific amount of solvent under defined temperature and pH conditions.[1] To absorb any drug it must be present at the absorption site in the form of an aqueous solution.[2-4] Drug absorption and bioavailability of drug substances administered orally relies heavily on solubility in aqueous media. Out of all new chemical entities, about 40% have poor water solubility. Such poorly water soluble drugs display a sluggish pattern of absorption of drugs leading to insufficient and variable bioavailability and toxicity of gastrointestinal mucosa.[5] Drugs having aqueous solubility smaller than 1µg/ml will surely create problem related to bioavailability. Since solubility and permeability are the key factor in the drug's in-vivo absorption, techniques for improving the solubility can enhance these. Bioavailability can be improved particularly for BCS class II drugs by increasing the dissolution rate and solubility of the drug in the GI fluids.[6]

Some medications such as Itraconazole and Carbamazepine and log P value 2 medications such as morphine, ketamine, diphenoxylate have significant absorption difficulties because these are least soluble in both organic and aqueous media. These drugs also have inconsistent absorption profile and highly variable bioavailability because their output is restricted in dissolution rate and is influenced by patient's fasting/ fed state.[7]

There have been a number of attempts to change the dissolution properties of some drug products to ensure more rapid and full absorption. The novel methods generally used for solubility enhancement of drug includes micronization, nanonization, super critical fluid method, spray freezing into liquids, sonocrystallization, hydrotropy method, solid dispersion, salt formation, co-

solvency, addition of solubilizing agents, complexation and pH adjustment. The methods are selected based on the physicochemical properties of the drug in question, the properties of the excipients to be used and the complexity of the dosage type. In screening studies of new chemical entities as well as in the design and development of formulations, the solubilization of poorly soluble drugs is often met with dispute. Drug solubility is expressed by different expression of concentration such as parts, percentage, molarity, molality, mole fraction etc.[8]

The solubility of drugs is classified into seven classes as per Indian Pharmacopoeia as listed in Table1.[9]

Table1: Solubility Description Table as per IP.

Sr. No.	Category	Parts of solvent required for part of solute
1	Very soluble	Less than 1
2	Freely soluble	From 1 to 10
3	Soluble	From 10 to 30
4	Sparingly soluble	From 30 to 100
5	Slightly soluble	From 100 to 1000
6	Very slightly soluble	From 1000 to 10,000
7	Practically insoluble, or insoluble	10,000 or more

Biopharmaceutics Classification System For Drugs[10]

The rate and extent of oral absorption of drug from solid dosage form type depends on two factors:

1. **Solubility:** The substance dissolves to prepare a solution.
2. **Permeability:** The dissolved drug is transferred through the gastrointestinal membrane.

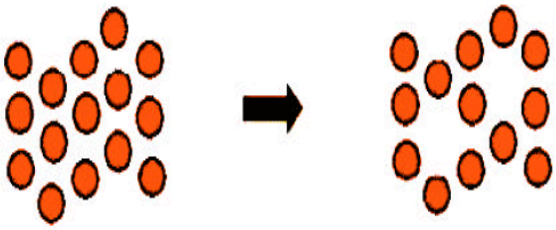
So based on these two factors of the drugs, Amidon *et al* developed Biopharmaceutics Classification System (BCS) according to which drugs are classified into 4 classes as shown in Table 2.

Table 2: Biopharmaceutical Classification of Drugs.

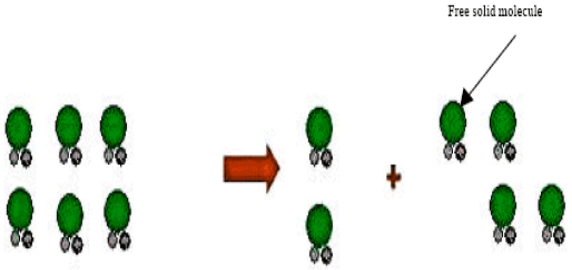
Class	Solubility	Permeability	Absorption	Rate limiting step in absorption	Example	Challenges in drug delivery
I	**High**	**High**	Well absorbed	Gastric emptying	Diltiazem Verpamil Propranolol Metoprolol	No major problem for immediate release dosage forms but controlled release forms have as drug absorption is rapid.
II	**Low**	**High**	Variable	Dissolution	Nifedipine Ketoconazole Mefenamic acid Naproxen	Formulations are designed to overcome solubility or dissolution problems.
III	**High**	**Low**	Variable	Permeability	Acyclovir Captopril Metformin Cimetidine	Approaches are employed to enhance permeability.
IV	**Low**	**Low**	Poorly absorbed	Case by case	Chlorthiazide Furosemide Meloxicam Taxol	Both strategies employed for class II and III drugs are used to improve both dissolution and intestinal permeability.

Process of Solubilisation

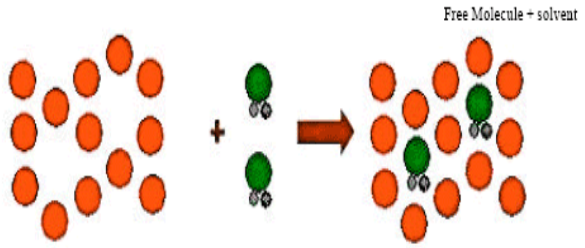
Solubilisation essentially involves three steps- separation of the solvent molecules to incorporate solute molecules, breaking of inter-ionic or intermolecular forces in the solute and contact between the solvent and the solute molecule or ion[11] as shown in Fig.1.



Step 1: Separation of the molecules of the solvent to incorporate solute molecules.



Step 2: Breaking of inter-ionic or intermolecular bonds in the solute.



Step 3: Contact between the solvent and the solute molecule or ion.

Figure 1: Diagrammatic Representation of Process of Solubilization.

Factors Affecting Rate Of Solubility

1. **Particle size of solute:** The dimension of the solid particles affect the solubility because particle size is inversely proportional to the surface area. Larger the surface area, greater the contact with solvent molecules.[12] The effect of particle size on solubility rate can be given by Eq.1.

$\log S/S_0 = 2\gamma M / 2.303 RT\rho r$……Eq.1

where,

S= solubility of small particles of radius r

S_0 = normal solubility

γ = interfacial energy

M = molecular weight of solid

ρ = density of the bulk solid

R = gas constant

T = temperature

r = radius of fine particle

2. **Molecular size:** Larger the molecular size of the molecule, lesser the substance's solubility. Bigger molecules are harder to surround with solvent molecules in order to remove the material. In case of organic compounds, more carbon branching will increase the solubility because further branching will decrease the molecule's size and make it easy to dissolve the solute molecules within the solvent.

3. **Nature of solute and solvent:** As we know "like dissolves like" so when two substances are identical they can dissolve easily in one another i.e. dissolve polar solute in polar solvents and dissolve non-polar solute in non-polar solvents. In polar solvents, ionic compounds are more soluble than in non-polar solvents.

Solute	Polar solvent	Non-polar solvent
Polar	Soluble	Insoluble
Non-polar	Insoluble	Soluble
Ionic	Soluble	Insoluble

Solvent purity and solute also influence the solubility. The presence of small quantities of impurities can either increase or reduce the solubility.

4. **Effect of Temperature:** The process of dissolution is typically heat absorption process i.e. heat is generally consumed as dissolution takes place. A rise in temperature in this type of system may lead to increase the solubility of solids with positive heat of solution. In comparison, in frequently occurring systems with exothermic dissolution, temperature change can result in lower solubility.[12]
5. **Effect of pressure:** In case of liquid and solid solutes, pressure variations have almost no effect on the solubility. With the application of pressure, the solubility is improved for gaseous solutions.
6. **Polymorphs:** When there is material that exist in crystalline forms more than one, then these different crystalline forms are called polymorphs. The melting point of the polymorphs can vary. Since the solids melting point is correlated with solubility, the various polymorphs of the same material would have different solubility. Owing to relatively small variations in the free energy, the solubility difference range between different polymorphs is usually only 2-3 times.
7. **Stirring:** As such the stirring has no effect on substance's solubility. It just speeds up the solubilisation process. Stirring increases movement that exposes solute to fresh portions of solvent thus allowing solubility. By stirring the chemical interaction between the solute and solvent molecules get increased.[12]

Need For Solubility Enhancement

Just 8 percent of the new drug candidates belongs to BCS Class I category that have high solubility and high permeability, according to recent figures. Upto 40 percent of new drug substances currently being discovered are completely insoluble in water. Many of the drugs mentioned in US Pharmacopoeia fall into the category of poorly water soluble. Poor aqueous solubility is the main problem facing the production of new chemical moieties for formulation. Since the solubility is one of the essential criteria for achieving desired drug concentration in blood circulation, a drug must be solubilized to exert its pharmacological response.

The factors responsible for poor aqueous solubility are:

1. Strong intermolecular interactions which complicate and energetically cost the solubilisation of solid particles.
2. High degree of lipophilicity.

The enhancement of drug solubility is always one of the most critical and challenging aspects of the long drug development process, particularly for oral drug delivery. There are different methods available to improve the solubility of medicines which have partial aqueous solubility. Some of them are discussed as follows:

Solubility Enhancement Techniques

There are many available strategies for enhancing the solubility of poorly soluble drugs. These techniques are categorized under following major classes.[13,14]

1. Physical Modifications

i. Particle size reduction

a. Micronization
b. Nanonization
c. Supercritical fluid recrystallization

ii. Modification of crystal habit-

a. Polymorphs
b. Pseudopolymorphs

iii. Drug dispersion in carriers-

a. Eutectic mixture
b. Solid dispersions
c. Solid solutions

iv. Solubilisation by surfactants

a. Microemulsions
b. Self emulsifying drug delivery system (SEDDS).

2. Chemical Modifications

- Salt formation
- Complexation
- Co-crystallisation
- Co-solvency
- Hydrotropy

Physical Modifications

Particle size reduction: The bioavailability of poorly soluble drugs is boosted up by reducing their particle size to sub-micron level. This can be done by the use of approaches to micronization or nanonization.

a. Micronization: Micronization requires decreasing the size of the solid drug particles from 1-10 microns. By that decreased particle size, the surface area is increased which improves the properties of drug's dissolution. Micronization may be achieved by spray drying or using methods of air attrition methods like fluid energy or jet mill. The method is also known as micro-milling. This technique is not ideal for drugs that have high dose number because it does not alters the drug's saturation solubility.[10,15,16]

Example: Drugs whose bioavailability has improved through micronization include Griseofulvin, a variety of steroidal drugs and Sulpha drugs.

b. Nanonization: It is a mechanism by which the powdered drug is processed into nanocrystals of between 200-600nm size range. Specific nanonization techniques have been utilized to improve the solubility and dissolution property and ultimately to improve the bioavailability of drugs. For new chemical entities with least aqueous solubility, solubility improvement by micronization is not sufficient because the micronized substance has the propensity to result in clump formation which leads to reduction of effective surface area, so the alternative method is nanonization. Three main technologies commonly used in the preparation of nanoparticles are pearl milling, homogenization in water, homogenization in non-aqueous media or in water with water- miscible liquids.[10]

Example: Drugs to which nanonization has increased their bioavailability include Tarazepide, Amphotericin B, Paclitaxel and Atovaquone.

c. Supercritical Fluid Recrystallization: Reduction of particle size via supercritical fluid method is another innovative technology for nanosizing and solubilisation, whose use has increased in recent years. Supercritical fluids have higher temperature and pressure than critical temperature (Tc) and critical pressure (Tp). They have the properties of both a liquid and a gas. Examples of supercritical fluid includes CO_2, N_2O, ethylene, propylene, ethanol, ammonia. Of such, most used is carbon dioxide and water, since it is safe, environment friendly and economical. When the drug particles are solubilized within super critical fluids, they can be recrystallized at much reduced particle size. Current SCF processes have the ability to produce nanosuspensions of 5-2000nm in diameter with wide surface areas, uniform controlled particle size and smooth surface finally raising the drug bioavailability.[10]

Various supercritical processes include[17] - particle formation from gas- saturated solutions (PGSS), rapid expansion of supercritical solutions (RESS), super critical anti solvent process (SAS), gaseous anti-solvent (GAS), aerosol solvent extraction system (ASES), precipitation with compressed anti-solvent (PCA), solution enhanced dispersion by supercritical fluid process (SEDS) etc.

Example: Drugs include Fluorouracil, Acetaminophen, Ampicillin, Amoxicillin, Felodipine, Carbamazepine, Indomethacin, Ketoprofen etc.

Modification of Crystal Habit: A drug's crystalline form is of medicinal significance from both the perspectives of stability and bioavailability. These types of crystalline forms of solid drug are polymorphs and pseudopolymorphs that can cause changes in melting point, density, stability and solubility of drugs. These must be addressed during preformulation studies to prevent further problems with solubility or stability.[6]

a. Polymorphs: Polymorphism is the capacity of chemical compound to crystallize in more than one crystalline form of an element or compound. Different drug polymorphs are chemically similar, yet have specific physical and chemical properties like solubility, melting point, density, texture, stability as such properties rely on the molecules' escape tendency from particular crystalline structure. As a rule, the lowest

amount of free energy holds the high melting point and the lowest solubility value for a substance that has the greater degree of crystallinity is the most stable form. It is possible to stabilize metastable or amorphous types of drugs showing high free energy by manipulating the crystallization process. By controlling the process of crystallization, metastable or amorphous forms of drugs showing high free energy can be created. They offer high solubility but have some stability issues which can be overcome by adding stabilizers in the formulation.[18]

The dissolution order for various solid forms of drug is
Amorphous > Metastable > Stable Polymorph

Example: 1. Riboflavin's polymeric form III is 20 times more soluble in water than form I.
2. Novoboicin in an amorphous form is 10 times more soluble than crystalline.

b. Pseudopolymorphs (hydrates/ solvates): The molecular adduct which integrates solvent molecules in the solid crystal lattice is called solvates. The solvates may exist in various crystalline forms and may be called pseudopolymorph and this phenomenon is called as pseudopolymorphism. If water is a solvent in conjunction with the product, the solvate is known as hydrate. The anhydrous form of the product has higher aqueous solubility than hydrates as hydrates have already integrated water molecules and therefore have less capacity for crystal breakup as opposed to anhydrous form. Additionally, organic solvates have more aqueous solubility than non-solvates.

Example
1. Anhydrous form of Theophylline have higher solubility in comparison to their monohydrate form.
2. Griseofulvin Chloroform solvates are more soluble in water than their non solvate form.

Drug Dispersion in Carrier: It refers to the dispersion in solid state of one or more active ingredients into an inert carrier. Hydrophilic carriers which are most widely used include polyvinyl pyrrolidone, polyethylene glycols etc. Dispersion of drugs are prepared using melting method, solvent method or solvent fusion process. New techniques include supercritical fluids and spray drying and rapid precipitation by freeze drying.[19]

a. Eutectic Mixture: A eutectic mixture is characterized as a mixture of two or more components that usually do not interact as such to form a new chemical compound but inhibit each other's crystallization process at certain ratios. This results in a system with a lower fusion point as compare to individual components**.**[20] The soluble carrier molecule dissolves when eutectic mixture comes into contact with water, leaving the drug in microcrystalline state that easily becomes solubilized. An eutectic mixture consists of two compounds which are immiscible in solid state but get completely miscible in the liquid state. Solid eutectic mixtures are typically prepared by fast cooling method to obtain a physical mixture of the two components with very fine crystals. The wide effective surface area of the formed suspension will lead to an increased rate of dissolution and thus to improved bioavailability.

Example: 1. Genistein and PEG 460 in ratio of 1:24 could help in injection development by solubilising Geinstein crystals.

2. Menthol and Poloxamer 188, Ibuprofen in ratio of 1:9 shows higher AUC as compared to a solid suppository.
b. Solid Dispersion: In 1961, solid dispersion approach was first recognized to increase the dissolution rate and absorption of drugs. Solid dispersion can defined as the dispersion in an inert excipient or matrix of one or more active ingredients where the active ingredients may exist in finely crystalline, soluble or amorphous state.[21] The mechanisms responsible for enhanced solubility and dissolution rate of solid dispersion drugs are as follows:

- Large surface area given by decrease in size of particles.
- Improved product wetting and dispersing properties.
- Particulate matter of greater porosity.
- Drugs in amorphous form.
- Solubilizing effect produced on the drug by water soluble carrier.

Example:
1. Nifedipine + Polyvinylpyrrolidone dispersion polymer.
2. Fenofibrate + polyethylene glycol
3. Itraconazole + HPMC

Solid dispersion can be prepared by various methods like co- precipitation, lyophilization, spray drying, melting solvent method, melt extrusion method, fusion method etc.

c. Solid Solutions: A solid solution is a binary compound consisting of a molecularly dispersed solid solute in a solid solvent. It is also known as mixed crystals or molecular dispersion. Solid solutions exhibit greater aqueous solubility and faster dissolution than eutectics and solid dispersion due to reduction in particle size to molecular level. They are usually prepared by fusion method in which mixture of solute and solvent is melted together and rapid solidification is followed by. Often called melts are solid solutions, prepared by fusion process.[22]

Example: Griseofulvin- succinic acid: Griseofulvin from such solution dissolves 6 to 7 times faster than pure Griseofulvin.

Solubilisation by Surfactants: Surfactants are substances that adsorb onto system's surface and interface and decrease the interfacial stress. With distinct polar and non-polar region, they have characteristic structure. In order to increase the solubility of poorly

soluble substance, the concentration of surfactants must be above the critical micelle concentration (CMC). Surfactants can be anionic, cationic and non-ionic in nature.[6] Various surfactants such as Tween, Spans, polysorbates, polyoxyethylated glycerides etc. are used to facilitate the dissolution of poorly soluble compounds.

a. Microemulsion: Microemulsion is an oil, water and surfactant system that forms a single, thermodynamically stable and optically transparent emulsion. These are water based formulations that typically have very small emulsified droplet size usually between 0.01-0.05µm rendering the formulation transparent. Microemulsions improve the solubility of many medications that are practically insoluble in water, along with protein incorporation for oral, parentral and percutaneous/ transdermal usage.[23] Surfactants, surfactants mixture and co-surfactants play a significant role in increasing the solubility microemulsion formulated products. The main downside of microemulsion is its high concentration of surfactant/cosurfactant which makes them unfit for IV administration.

Example: Drugs whose solubility improved by preparing microemulsion are Tipranavir (HIV protease inhibitor) and cyclosporine A (immunosuppressant)[24]

b. Self Emulsifying Drug Delivery System (SEDDS): Self emulsifying drug delivery system has unprecedented potential to boost the oral bioavailability of drugs that ae poorly soluble in water. Such systems immediately disperse after oral administration in gastrointestinal fluids that produce micro or nanoemulsions containing the solubilized drug.

Owing to the relatively small size of the globule, the micro/ nanoemulsified drug can be readily absorbed through lymphatic channels, bypassing the hepatic first pass effect.[25]

Since SEDDS contains high surfactant concentrations, they should be limited to oral applications and may not be recommended for long term use due to the potential to cause diarrhoea.

Example: The relative bioavailability of cyclosporine A administered as SMEDDS may account for 174-239 percent of the bioavailability of cyclosporine A from the formulation originally marketed.[24]

2. Chemical Modifications

Salt Formation: Salt formation has enhanced the characteristics of solubility and dissolution as compared to the original drug. Typically a minimum difference of 3 units is required between the group's pKa value and that of its counterion is required to form stable salts. The primary salt formation prerequisite is that the drug should have ionizable groups that will assist in salt formation. The criterion used to pick counter ion is as follows:

- Difference of 2-3pKa units between drug and counter ion should be atleast.
- Counter ion should decrease crystal lattice forces.
- It requires approval by FDA.[26]
- But this method of improving dissolution has some limitations:
- The formation of salt of neutral compounds practically not feasible.
- Salts with very low acids and bases are hard to form.
- The salt may be hygroscopic, may exhibit polymorphism or may have poor processing characteristics.[10]

Example: 1. Alkali metal salts of acidic drugs such as Penicillin and strong acid salts of basic drugs such as Atropine are more water soluble than parent drug.

2. Tetracycline hydrochloride, Diclofenac sodium have better solubility than parent drug.

ii. Complexation: The use of complex formation techniques has been more explicitly employed among the various numerous techniques of solubility enhancement to improve the aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs. Inclusion complexes are created by the inserting the non-polar molecule or the non-polar region of one molecule (called guest) into the cavity of another molecule or group of molecules (called host). The host molecules which are most widely used are cyclodextrins.[27]

Cyclodextrins are non reducing, crystalline, water soluble, and cyclic oligosaccharides composed of glucose monomers arranged in a donut shaped ring with hydrophobic cavity and hydrophilic outer surface. Three CDs that exist naturally are α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin.[28] The cyclodextrin molecule's surface makes them water soluble, but the hydrophobic cavity provides a microenvironment for suitably shaped non-polar molecules.

Example: 1. With the use of cyclodextrin inclusion complex, the solubility as well as oral bioavailability of Piroxicam, Rofecoxib, Glipizide and Carvedilol can be enhanced.

2. Rifampicin-CD inclusion compound when given as aerosolized solution will enhance lung transport of drug.

Co-Crystallisation: Co-crystallization is a common method capable of enhancing the physicochemical properties of the drug such as solubility, dissolution rate, bioavailability, and stability.[29] It can be applied to any type of compound like acidic, alkaline, neutral and ionic compounds.[30] The technique is commonly used to alter the characteristics of a pharmaceutical drug compound and thus to change it into a compound with the desired characteristics.[31] Co-crystal is becoming an essential class of pharmaceutical solid that by forming a complex crystal, can increase the solubility and dissolution of the API. It consists of a drug and co-crystal former (co-former) with a given defined stoichiometric ratio and linked by a synthon.[32] A synthon is a non-covalent interaction involving the hydrogen bonds, Vander Waals, and π-π electrons. Synthon interaction can be expected via the in silico system. It is always advantageous to

know the kind of API and co-former interaction. A variety of techniques were to synthesize co-crystals such as melting extrusion, ultrasonic slurry formation, particle size reduction, spray drying and solvent evaporation.[33]
Example: Co-crystals of Carbamazepine, Fluoxetine hydrochloride, Itraconazole, Sildenafil, Theophylline, Aceclofenac, 5-fluorouracil, Indomethacin provide improved solubility.[34]

Co-Solvency: Co-solvency is another popular approach in pharmaceutical liquid dosage forms to increase the solubility of poorly water soluble drugs.[35] Cosolvents consists of water miscible solvents that can dramatically alter the solubility of poorly water soluble drugs.[36] Through incorporating any water miscible solvent in which the product has strong solubility , the solubility of poor electrolytes and non polar molecules can be increased. This process of adding water miscible solvent is known as cosolvency, and the solvent used for it is known as cosolvent. Cosolvent system works by decreasing the stress between the water and hydrophobic solute. It is widely referred to as solvent blending.[36] Cosolvents have both donor and/or acceptor groups of hydrogen bond as well as small hydrocarbon regions. Responsible for water miscibility is their hydrophilic hydrogen-bonding groups, whereas their hydrophobic hydrocarbon regions interfere with water bonding network. Cosolvents minimize the ability of water to extract nonpolar, hydrophobic compounds and thereby increase the solubility.[37] Cosolvent technology has advantages of simplicity, safety, preventing contamination in the dispensing process, affordable, no need for costly pharmaceutical technology for medication formulation.[38] Polyethylene glycol, dimethylsulfoxide, and dimethylacetoamide, propylene glycol, ethanol, glycerin are widely used cosolvents for parenteral usage.[39-43]

Example: Simvastatin, Lornoxicam, Etoricoxib, Diazepam, Etoposide, 5-fluorouracil, Erythromycin, Chloramphenicol.

Hydrotropy: Neuberg first coined hydrotropy to explain the increase in the aqueous solubility of BCS Class II molecules by the introduction of high concentrations of alkali metal salts of different organic acids. It is a solubilization process in which addition of significant quantity of hydrotropic agent results in an improvement in first solute aqueous solubility. Hydrotropic agents are typically ionic organic salts, composed of alkali metal salts of various organic acids. Additives which increase the solubility in given solvent are said to “salt in” the solute and those salts which decrease solubility “salt out” the solute. The mechanism by which this technique increases the solubility is almost same as that of complexation involving interaction between the hydrotropic agents such as sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs.[44-45]
The hydrotropes in solution are used to self-assemble. In addition to improving the solubilization of compounds in water, they also influence aggregation of surfactants that lead to miceller formation, clouding of polymers and surfactants etc.[46]

Example: Cefprozil, Cefadroxil, Furosemide, Hydrochlorothiazide, Salicylic acid, Nifedipine, Ketoprofen.

CONCLUSION

A drug’s therapeutically effective concentration at the target action site depends on the bioavailability, which ultimately depends on the solubility of the drug molecule. Solubility is one of the significant and crucial factor necessary to achieve the effective concentration of drug in systemic circulation to elicit therapeutic effect. Since dissolution of drug is the rate determining stage for oral bioavailability of the poorly soluble drugs, the various methods as mentioned above can be employed either individually or in combination to improve the drug solubility. Selection of appropriate method is the key point for the enhancing the solubility of hydrophobic medicinal products. The method selection should depends on the quality of the drug, its effectiveness, its association with other chemicals compounds that are used, reliability when the process is performed and the end product yield. At the same time, account should be taken of economic factor when choosing either of the methods.

REFERENCES

1. Satish KP, Kalpesh SW, Venkatesh BP, Anup MA, Dheeraj TB. Strategies for solubility enhancement of poorly soluble drugs. International Journal of Pharmaceutical Sciences Review and Research, 2011; 8(2): 74-80.
2. Shargil L & Yu. Applied Biopharmaceutics. Appleton-century crofts, Norwalk, 1985; 2: 193-203.
3. Martin A. Physical Pharmacy. Lippincott Williams & Wilkins. A Walters Kluwer Co. Philadelphia, 5th edition, 2003: 410-418.
4. Meyer MC. Bioavailability of drugs and bioequivalence In: Encyclopedia of Pharmaceutical Technology. New York. Marcel Dekker Inc, 1998; 2: 33-58.
5. Rinaki E, Valsami G, Macheras P. Quantitative Biopharmaceutics classification system: the central role of dose/solubility ratio. Pharm. Res., 2003; 20:1917.
6. Ahmad Z, Maurya N, Mishra K, Khan I. Solubility enhancement of poorly water soluble drugs: a review. International Journal of Pharmacy and Technology, 2011; 2(1): 807-23.
7. Gaikwad SS, Mhalaskar RS, Mahale YD, Jain NP. Review on Solubility enhancement of poorly water soluble drug. Indo American Journal of Pharmaceutical Research, 2014; 4(11): 5530-5541.

8. Vemula V, Lagishetty V, Lingala S. Solubility enhancement techniques. International Journal of Pharmaceutical Sciences Review and Research, 2010; 5(1): 41-51.
9. Indian Pharmacopoeia, Controller of Publication, Govt. of India, Ministry of Health and Family Welfare, New Delhi, 2014; 1,2.4.26: 174.
10. Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics, Vallabh Prakashan, 2009: 345-357.
11. Chaudhary A, Nagaich U, Gulati N, Sharma V, Khosa R. Enhancement of solubilisation and bioavailability of poorly soluble drugs by physical and chemical modifications: a recent review. Journal of Advanced Pharmacy Education and Research, 2012; 2(1): 32-67.
12. Aulton ME. Pharmaceutics- The design and manufacture of medicines. 3rd edition, Churchill Livingstone, London, 25-28.
13. Chaumeil JC. Micronisation: A method of improving the bioavailability of poorly soluble drugs. Methods and findings in experimental and clinical pharmacology, 1998; 20(3): 211-215.
14. Patel RP, Baria AH, Patel NA. An overview of size reduction technologies in the field of pharmaceutical manufacturing. Asian journal of Pharmaceutics, 2008; 2(4): 216-220.
15. Vandana KR, Raju YP, Chowdary VH, Sushma M, Kumar NV. An overview on in situ micronization technique- An emerging novel concept in advanced drug delivery. Saudi Pharmaceutical Journal, 2014; 22: 283-289.
16. Pant P, Bansal K, Rama P, Therdana R, Padhee K, Sathapathy A, Singh KP. Micronization: an efficient tool for dissolution enhancement of Dienogest. International Journal of Drug Development & Research, 2011; 3(2): 329-333.
17. Kankala RK, Zhang YS, Wang SB, Lee CH, Chen AZ. Supercritical fluid technology: An emphasis on drug delivery and related biomedical applications. Adv. Healthcare Mater, 2017; 6: 1-31.
18. Chaudhary A, Nagaich U, Gulati N, Sharma VK, Khosa RL. Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review. Journal of Advanced Pharmacy Education & Research, 2012; 2(1): 32-67.
19. Craig DQM. The mechanisms of drug release from solid dispersion in water soluble polymers. Int J Pharm, 2002; 203: 131-144.
20. Stott PW, Williams AC, Barry BW. Transdermal delivery from eutectic systems: Enhanced permeation of a model drug Ibuprofen. J Control Release, 1998; 50: 297-308.
21. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci, 1971; 60: 1281-1302.
22. Wirkar S, Gaud R. solid dispersions: solubility enhancement technique for poorly soluble drugs. International journal of research in pharmaceutical and biomedical sciences, 2013; 4(3): 847-854.
23. Jayne LM, Rees GD. Microemulsion based media as novel drug delivery systems. Adv. Drug Deliver. Rev., 2000; 45(1): 89-121.
24. Mueller EA, Kovarik JM et al. Improved dose linearity of cyclosporine pharmacokinetics from a Microemulsion formulation. Pharmaceutical research, 1994; 11(2); 301-304.
25. Singh B, Bandopadhyay S, Kapil R, Singh R, Katare O. Self emulsifying drug delivery systems (SEDDS): Formulation, development, characterization and applications. Crit Rev Ther Drug Carrier Syst, 2009; 26(5): 427-521.
26. Thorat Y, Gonjari D, Hosmani A. Solubility enhancement techniques: a review on conventional and novel approaches. International Journal of Pharmaceutical Sciences and Research, 2011; 2(10): 2501-13.
27. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins and drug solubilization and stabilization. Journal of Pharmaceutical Sciences, 1996; 85:1017-25.
28. Uekama K, Hirayama F, Irie T. Cyclodextrin drug carrier systems, Chemical Reviews, 1998; 98(5): 2045–2076.
29. Miroshnyk I, Mirza S, Sandler N. Pharmaceutical co-crystals- an opportunity for drug product enhancement. Expert Opin Drug Deliv, 2009; 6(4): 333-41.
30. Aakeroy CB, Fasulo M, Schultheiss N, Desper J, Moore C. Structural competition between hydrogen bonds and halogen bonds. J Am Chem Soc, 2007; 129(45): 13772-3.
31. Boetker J, Raijada D, Aho J, Khorasani M, Sogaard SV, Arnfast LE. In silico product design of pharmaceuticals. Asian J Pharm Sci, 2016; 11(4): 492-9.
32. Crivori P, Morelli A, Pezzetta D, Rocchetti M, Poggesi I. Development and validation of in silico models for estimating drug preformulation risk in PEG400/water and Tween80/water systems. Eur J Pharm Sci, 2007; 32(3): 169-81.
33. Boksa K, Otte A, Pinal R. Matrix-Assisted Co-crystallization (MAC) Simultaneous Production and Formulation of Pharmaceutical Co-crystals by Hot-Melt Extrusion. J Pharm Sci, 2014; 103(9): 2904-10.
34. Yadav AV, Shete AS et al. Co-Crystals: A Novel Approach to Modify Physicochemical Properties of Active Pharmaceutical Ingredient. Ind J Pharm Sci, 2009; 71(4): 359-370.
35. Amin K, Dannenfelser RM, Zielinski J, Wang B. Lyophilization of polyethylene glycol mixtures. Journal of Pharmaceutical Sciences, 2004; 93(9): 2244–2249.
36. Yalkowsky SH and Roseman TJ. Solubilization of drugs by cosolvents in Techniques of Solubilization of Drugs, Dekker, New York, USA, 1981.
37. Millard JW, Alvarez-Nunez FA, and Yalkowsky SH. Solubilization by cosolvents: establishing useful

constants for the log-linear model. International Journal of Pharmaceutics, 2002; 245(1-2): 153–166.
38. Yeh MK, Chang LC, Chiou HJ. Improving Tenoxicam solubility and bioavailability by cosolvent system. AAPS Pharm Sci Tech, 2009; 10(1): 166–171.
39. Babu PR, Subrahmanyam CV, Thimmasetty J, Manavalan R, Valliappan K and Kedarnath SA. Solubility enhancement of COX-II inhibitors by cosolvency approach. Journal of Pharmaceutical Sciences, 2008; 7(2): 119–126.
40. Yalkowsky SH, Rubino JT. Solubilization by cosolvents: organic solutes in propylene glycol-water mixtures. Journal of Pharmaceutical Sciences, 1985; 74(4): 416–421.
41. Pan L, Tsutsui K, Takahashi L et al. Comparison of chromatographic and spectroscopic methods used to rank compounds for aqueous solubility. Journal of Pharmaceutical Sciences, 2001; 90(4): 521–529.
42. Nema S, Washkuhn RJ, Brendel RJ. Excipients and their use in injectable products. PDA Journal of Pharmaceutical Science and Technology,1997; 51(4):166–171.
43. Rubino JT, Yalkowsky SH. Co-solvency and deviations from log-linear solubilization. Pharmaceutical Research, 1987; 4(3): 231–236.
44. Sunkara G, Kompella UB. Drug delivery applications of supercritical fluid technology. Drug Delivery Technology, 2002; 2: 44–50.
45. Manna L, Banchero M, Sola D, Ferri A, Ronchetti S, and Sicardi S. Impregnation of PVP microparticles with ketoprofen in the presence of supercritical CO_2. Journal of Supercritical Fluids, 2007; 42(3): 378–384.
46. Roy BK, Moulik SP. Functions of hydrotropes (sodium salicylate, proline, pyrogallol, resorcinol and urea) in solution with special reference to amphiphile behaviors. Colloids and Surfaces A: Physicochemical and Engineering Aspects, 2002; 203(1–3): 155–166.