

## Review Article

**BIOAVAILABILITY ENHANCEMENT FOR POORLY SOLUBLE DRUGS: A REVIEW**CHINMAYA KESHARI SAHOO<sup>1</sup>, G. SANTHOSHINI REDDY<sup>2</sup>, BUCHANPALLY VIKRAM REDDY<sup>2</sup>, ABHIGNYA VOJJALA<sup>2</sup><sup>1</sup>Assistant Professor, Department of Pharmaceutics, Malla Reddy College of Pharmacy (affiliated to Osmania University), Hyderabad, Telangana, India. <sup>2</sup>UG Scholar, Department of Pharmaceutics, Malla Reddy College of Pharmacy (affiliated to Osmania University), Hyderabad, Telangana, India.

Email: ssherif14@yahoo.com, ssherif14@azhar.edu.eg

**ABSTRACT**

**Objective:** The main objective is to describe the techniques of solubilization for the attainment of effective absorption and improved bioavailability. **Methods and Sources:** Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. Drug with poor water solubility cause slow dissolution rates, generally show erratic and incomplete absorption leading to low bioavailability when administered orally. The details about the different approaches used for the enhancement of the solubility of poorly water-soluble drugs were discussed. **Conclusion:** Bioavailability of poorly water soluble drugs can be enhanced by choosing suitable technique.

**Keywords:** Solubility, bioavailability, absorption, solubilization.**INTRODUCTION**

Solubility is defined in quantitative terms as the concentration of solute [1] in a saturated solution at a certain temperature, and in a qualitative way, it can be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. The solubility of a compound depends on the physical and chemical properties of the solute and the solvent as well as on such factors as temperature, pressure, the pH of the solution etc. Thermodynamic equilibrium solubility is achieved when the overall lowest energy state of the system is achieved. The *United States Pharmacopeia (USP)* describes the solubility of drugs as parts of solvent required for one part solute. Solubility is also quantitatively expressed in terms of molality, molarity, and percentage. The USP describes solubility using the seven groups listed in Table 1.

**Table 1: According to USP solubility expressions**

Solubility	Part of solvent required for 1 part of solution	Solubility range (mg/ml)	Solubility assigned (mg/ml)
Very soluble	<1	>1000	1000
Freely soluble	From 1 to 10	100-1000	100
Soluble	From 10 to 30	33-100	33
Sparingly soluble	From 30 to 100	10-33	10
Slightly soluble	From 100 to 1000	1-10	1
Very slightly soluble	From 1000 to 10,000	0.1-1	0.1
Practically insoluble	>10000	<0.1	0.01

**Table 2 Biopharmaceutical Classification System (BCS)**

BCS Class I	High solubility/High permeability	B-blockers propranolol, Metoprolol
BCS Class II	Low solubility/High permeability	NSAID's Ketoprofen, Antiepileptic Carbamazepine
BCS Class III	High solubility/Low permeability	H2 antagonist Ranitidine
BCS Class IV	Low solubility/Low permeability	Diuretics Hydrochlorothiazide, frusemide

**Need of solubility**

When administered an active agent orally it must first dissolve in gastric or intestinal fluids before it can permeate the membranes of the GIT to reach systemic circulation. 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. Biopharmaceutical Classification System (BCS) is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability is discussed in Table-2.

**Bioavailability**

The term bioavailability [2] of drug is used to describe the fraction of an administered dose of unchanged drug that reaches the systemic circulation. When a drug is administered intravenously, its bioavailability is 100%. However, when a medication is administered via other routes (such as oral), its bioavailability decreases (due to incomplete absorption or first-pass metabolism). Bioavailability indicates the rate and extent at which the active pharmaceutical ingredient is absorbed from the drug product and becomes available at the site of action. It is expressed as either absolute or relative bioavailability.

**Absolute bioavailability**

Absolute bioavailability measures the availability of the active drug in systemic circulation after non-intravenous administration (i.e. after oral, rectal, transdermal, and subcutaneous administration). The absolute bioavailability is the dose-corrected area under curve (AUC) non-intravenous divided by AUC intravenous. Therefore, a drug given by the intravenous route will have an absolute bioavailability of 1 (F=1) while drugs given by other routes usually have an absolute bioavailability of less than one.

**Relative bioavailability**

This measures the bioavailability of a certain drug when compared with another formulation of the same drug, usually an established standard, or through administration via a different route. When the standard consists of intravenously administered drug, this is known as absolute bioavailability.

**Reasons of poor bioavailability [3]****Poor aqueous solubility**

The contents of gastrointestinal tract are aqueous and hence a drug having poor aqueous solubility has a low saturation solubility which is typically correlated with a low dissolution velocity, resulting in poor oral bioavailability.

**Inappropriate partition coefficient**

Too hydrophilic drugs would not be able to permeate through the gastrointestinal mucosa and too lipophilic drug will not dissolve in the aqueous gastrointestinal contents. For optimum absorption, the drug should have sufficient aqueous solubility to dissolve in the gastrointestinal contents and also adequate lipid solubility to facilitate its partitioning into the lipoidal membrane and then into systemic circulation. Drugs having partition coefficient (log P) value in the range of 1 to 3 shows good passive absorption across lipid membranes.

**First-pass metabolism**

Orally administered drugs must pass through the intestinal wall and then through the portal circulation to the liver; both are common sites of first pass metabolism (metabolism of a drug before it reaches systemic circulation). Thus, many drugs may be metabolized before adequate plasma concentrations are reached resulting in poor bioavailability.

**Degradation in the gastrointestinal tract [4]**

Drug substances used as drugs have diverse molecular structures, prone to many and variable degradation pathways.

**Degradation due to low pH in stomach**

Most drug substances are fairly stable at the neutral pH values found in the small intestine, but unstable at low pH values found in the stomach. Examples of drugs that are very acid-labile are various penicillins, and erythromycin.

**Degradation due to chemical reactions taking place in stomach**

Possible degradation pathways include hydrolysis, dehydration, isomerization and racemization, elimination, oxidation, photodegradation, and complex interactions with excipients, food and other drugs. A hydrolytic cleavage takes place particularly at low pH of the stomach.

**Enzymatic degradation of drug in gastrointestinal tract**

Various classes of drugs such as therapeutic peptides and nucleic acids are enzymatically degraded by proteases/peptidases and nucleases, respectively. Ester bonds are cleaved by esterases such as lipases and proteases/peptidases exhibiting also esterase activity. Teriparatide undergoes enzymatic degradation in the intestinal mucosa by enzymes like trypsin, chymotrypsin and pepsin.

**Interaction with food**

Drugs that undergo a significant first-pass metabolism with a lower bioavailability ranging from 5% to 30% may be affected to a greater degree by grapefruit juice. Calcium as well as food and dairy products containing high concentrations of calcium, may decrease the absorption of tetracyclines due to chelate formation in the gut.

**Drug efflux pumps like p-glycoprotein**

Pglycoprotein plays a major physiological role in absorption, distribution and excretion of xenobiotics. Apical expression of P-glycoprotein in such tissues like liver, kidney and intestine results in reduced drug absorption from the gastrointestinal tract and enhanced drug elimination into bile and urine.

**Insufficient time for absorption**

If the drug (eg. highly ionized and polar drugs) does not dissolve readily or cannot penetrate the epithelial membrane during its residence time in the gastrointestinal tract, its bioavailability tends to be highly variable.

**Methods for improving bioavailability [5-25]**

Methods can be categorized in three basic approaches:

1. Traditional techniques
2. Newer and novel techniques
3. Vesicular approaches

**Traditional techniques****Co-solvency**

The addition of a water-miscible or partially miscible organic solvent is a common and an effective way to increase the solubility of a non-polar drug. This process is known as co-solvency and the solvents used in combination to increase the solubility of the drugs are known as co-solvents. The co-solvent system will work by reducing the interfacial tension between the predominately aqueous solution and the hydrophobic solute. Co-solvents such as ethanol, propylene glycol, glycerin, sorbitol and polyoxyethylene glycols can be used.

**Co-crystallization**

It is known 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 (inclusion complex). A co-crystal may be defined as a crystalline material that consists of two or more molecular (and electrically neutral) species held together by non-covalent forces. Co-crystals are more stable, particularly as the co-crystallizing agents are solids at room temperature.

**Hydrotropy**

Hydrotropy is a solubilization process whereby addition of bulky amounts of a second solute (Hydrotropic agents) results to enhance in the aqueous solubility of another solute. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to "salt in" the solute and those salts that decrease solubility salt out the solute. Several salts with large anions or cations that are themselves very soluble in water results in salting in of non-electrolytes called hydrotropic salts a phenomenon known as hydrotropism. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water soluble drugs.

**Micronization**

The process involves reducing the size of the solid drug particle to 1 to 10 microns commonly by spray drying or by use of air attrition methods such as fluid energy mill, jet mill, colloid mill etc.. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug due to the tendency of agglomeration, which leads to decreased effective surface area for dissolution.

**Alteration of pH of solvent**

By applying a pH change poorly water soluble drugs with parts of the molecule that can be protonated (base) or de-protonated (acid) may potentially be dissolved in water. While the importance of critical parameters like salt selection and pH adjustment has been stressed on pre-formulation, the use of pH altering excipients within drug delivery systems is also of significant utility.

**Change in dielectric constant of solvent**

The addition of a co-solvent can increase solubility of hydrophobic molecules by reducing the dielectric constant of the solvent. Due to the nature of hydrogen bonding, water is a good solvent for polar molecules and has a high dielectric constant. The dielectric constant is a measure of the effect a substance on the energy needed to separate two oppositely charged bodies. The energy required to separate two oppositely charged bodies is inversely proportional to the dielectric constant of the medium. Changes in dielectric constant of the medium may have a dominant effect on the solubility of the

ionizable solute in which higher dielectric constant can cause more ionization of the solute and results in more solubilization.

#### Use of surfactants

The presence of surfactants lowers the surface tension and increase the solubility of the drug within an organic solvent. Surfactants are amphiphilic in nature having a polar end (the circular head) and non-polar end (the tail). Small molecules of polar molecules can be accumulated into hydrophobic core of micelles. When a surfactant is placed in water, it will form micelles. A non-polar drug will partition into the hydrophobic core of the micelle and the polar tails will solubilize the complex.

#### Amorphous form

In amorphous forms atoms or molecules are randomly placed and have higher thermodynamic energy than corresponding crystalline forms. Generally amorphous form having more surface area than crystalline form and eventually increases the dissolution rate.

#### Salt formation

Salt formation of poorly soluble drug candidates (weak acids and bases) has been a strategy for several decades to enhance solubility. It is an effective method in parenteral and other liquid formulations, as well as in solid dosage forms. The aqueous solubility of an acidic or basic drug as a function of pH dictates whether the compound will form suitable salts.

#### Complexation

Complexation is the association between two or more molecules to form a non-bonded entity with London forces, hydrogen bonding and hydrophobic interactions. There are many types of complexing agents and major three are stacking complexation, inclusion complexation and cyclodextrin inclusion complexes.

#### Stacking complexation

Stacking 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 and cause some molecules to minimize the contact with water by aggregation of their hydrocarbon moieties. This aggregation is favored by large planar non-polar regions in the molecule. Stacked complexes can be homogeneous or mixed. The former is known as self-association and later as complexation.

#### Inclusion complexation

Inclusion complexes are formed by the insertion of the non-polar molecule or the non-polar 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 comfortable fit of the guest into the cavity of host molecule. The cavity of host molecule must be large enough to accommodate the guest and small enough to eliminate water as well, so that the total contact between the water and the non-polar regions of the host and the guest is reduced.

#### Cyclodextrin inclusion complexes

Cyclodextrins (CD) are bucket shaped cyclic oligosaccharides composed of 6-8 dextrose units ( $\alpha$ ,  $\beta$ ,  $\gamma$  CD) respectively joined through C-C double bonds. The interior of these molecules is lipophilic and exterior of these molecules is hydrophobic. Lipophilic molecules can be incorporated into interior cavity of CD leading to better stability, high water solubility, and increased bioavailability or decreased undesirable side effects. The presence of hydroxyl groups on the external surface of the CD molecule increases the possibility of hydrogen bonding with the drug molecules resulting in the formation of non-inclusion complexes as well.

#### Use of hydrates or solvates

A crystalline compound may contain either a stoichiometric or non-stoichiometric adducts such as inclusions, involve entrapped solvent molecules within the crystal lattice. A stoichiometric adducts

normally referred to as solvate and is a molecular complex that has incorporated the crystallizing solvent molecules into specific sites within the crystal lattice. When the incorporated solvent in water, the complex is called as hydrate. A compound not containing any water within its crystal structure is termed anhydrous. Aqueous solubilities of anhydrous forms are higher than the hydrate forms.

#### Use of soluble prodrugs

Prodrug strategy involves the inclusion of polar or ionizable moiety into the parent compound to improve aqueous solubility. The chemical decomposition and presystemic metabolism is to be reduced by the use of prodrug approach.

#### Ultrasonic waves

Solubility can be improved by the use of ultrasonic vibrators. An oscillator of high frequency (100-500 KHz) is used and the device is known as Pohlman whistle.

#### Functional polymer technology

Functional polymers enhance the dissolution rate of poorly soluble drugs by avoiding the lattice energy of the drug crystal, which is the main barrier to rapid dissolution in aqueous media. These polymers are ion exchange materials which contain basic or acidic groups that interact with the ionizable molecules of the surrounding medium and exchange their mobile ions of equal charge with surrounding medium reversibly and stoichiometrically. The resultant complex known as resinates can be formulated as a suspension, dry powder or tablet.

#### Controlled precipitation technology

Here the drug is dissolved in a water miscible organic solvent and then dissolved into aqueous medium containing stabilizers (HPMC, cellulose ethers, gelatin). The solvent dissolves in water and causes precipitation of the drug in the form of micro-crystals. Here the stabilizers control particle growth and enhance the dissolution rate of poorly soluble drug due to large surface area hydrophilized by the adsorbed stabilizer.

#### Evaporative Precipitation in Aqueous Solution (EPAS)

The EPAS process utilizes rapid phase separation to nucleate and produce nanoparticles and microparticles of lipophilic drugs. The drug is first dissolved in a low boiling point organic solvent, and solution is pumped through a tube where it is heated under pressure to a temperature above the solvents boiling point, and then sprayed through a fine atomizing nozzle into a heated aqueous solution. Surfactants are added to the organic solution and aqueous solution to optimize particle formation and solubilization as well.

#### Use of precipitation inhibitors

A significant increase in free drug concentration above equilibrium solubility results in supersaturation, which can lead to drug precipitation or crystallization this process also call as anti-nucleation. This can be prevented by use of inert polymers such HPMC, PVP, PVA, PEG etc. which act as precipitation inhibitors by one or more of the mechanisms

Increase the viscosity of crystallization medium thereby reducing the crystallization rate of drugs.

Provide a steric barrier to drug molecules and inhibit crystallization through specific intermolecular interaction on growing crystal surfaces.

Absorb onto faces of host crystals, reduce the crystal growth rate of the host and produce smaller crystals.

#### Solvent Deposition

In this technique, the poorly aqueous soluble drugs is dissolved in an organic solvent like alcohol and deposited on an inert, hydrophilic, solid matrix such as starch or microcrystalline cellulose followed by evaporation of solvent. This method is readily adaptable for thermolabile drugs and carriers.

### Spherical agglomeration

It is a particle engineering technique. It is combine unite process of crystallization, agglomeration and spheronization, which convert fine crystal in spherical shape particle. This technique is significant for improving the flow property like wettability and dissolution rate of poorly soluble drug. Amount of addition of spherical liquid, temperature and agitation speed parameter must be optimized in this technique for production of spherical crystal.

### Newer and novel methods

#### Nanoparticle technology

Nanotechnology will be used to improve drugs solubility by increasing the surface area. Oral bioavailability enhancement in some new chemical entities of very low solubility can be achieved by nanonisation technology.

#### Nanocrystal technology

The nanocrystallization is defined as a way of decreasing the drug particles to the size range of 1-1000 nanometers. There are two distinct methods such as bottom-up development and top-down development. In bottom-up method, nanoscale materials are chemically composed from atomic and molecular components to nanosized particles by precipitation and cryo-vacuum method. The top-down methods will be done by milling and high pressure homogenization down from micron sized particles.

#### Nanosuspensions technology

Nanosuspensions are very finely dispersed solid particles in aqueous vehicle, size distribution of solid particles with average particle size range of 200-600 nm. Here the bioavailability is improved by increase in surface area and saturation solubility aided by particle size reduction. These are prepared by using high pressure homogenization, precipitation and pearl milling.

#### Precipitation

Here poorly aqueous soluble drug is dissolved in a suitable organic solvent followed by its rapid mixing with a nonsolvent to effect precipitation of drug in nanosize particles. The product so prepared is also called as hydrosol. Hydrosols are colloidal aqueous suspensions containing drug nanoparticles of poorly water soluble drugs for intravenous administration. In precipitation technique the drug is dissolved in a solvent where it dissolve more which is then added to anti-solvent to precipitate the crystals in terms of nanoparticles. These nanocrystals can be removed from the solution by filtration and then dried in air.

#### High pressure homogenization

In high pressure homogenization is an aqueous dispersion of the crystalline drug particles is passed with high pressure through a narrow homogenization gap with a very high velocity. Here the principle is based on the cavitation forces within the particles are adequately high to convert the drug microparticles into nanoparticles. The particle size obtained during the homogenization process depends mainly on the nature of the drug, the pressure applied and the number of homogenization cycles as well.

#### Cryo-vacuum method

Cryo-vacuum method is to generate the drug substance nanoparticles by using liquid nitrogen. The active ingredient to be nanonized is first dissolved in water to attain a quasi-saturated solution and then sudden cooling of a solvent by immersing the solution in liquid nitrogen (-196 °C). Here rapid cooling causes a very fast rise in the degree of saturation based on the degree of solubility and development of ice crystals when the temperature drops below 0 °C and also this leads to a fast nucleation of the dissolved substance at the edges of the ice crystals.

#### Spray freezing into cryogenic fluids (SFL)

The SFL particles produce amorphous nanostructured aggregates of drug powder with high surface area and good wettability by liquid –

liquid impingement between the atomized feed solution and cryogenic liquid. In this method 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 vapour over liquid (SFV/L)

Freezing of drugs solution in cryogenic fluid vapors and consequent removal of frozen solvent will produces fine drug particles with high wettability called SFV/L. During SFV/L the atomized droplets typically start to freeze in the vapor phase 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.

#### Sonocrystallisation

The novel move toward particle size reduction on the basis of crystallisation by using ultrasound-assisted is called sonocrystallisation. Melt sonocrystallization is an novel particle engineering technique to enhance dissolution of hydrophobic drugs and to study its effect on crystal properties of drug.

#### Plasma Irradiation

Plasma is a partially ionized gas that contains an equal number of positive and negative ions and unionized neutral species such as molecules, atoms, and radicals. This is the possible technique for increasing the dissolution rate of poorly soluble drugs. It is created by subjecting a gas (e.g. O<sub>2</sub>) to a radio-frequency potential in a vacuum chamber and thus leads to the production of electrons which are accelerated by an electric field and collide with neutral molecules to produce free radicals, atoms, and ions. During plasma treatment oxygen radicals produced by irradiation plasma then react with the chemical groups on the surface of an exposed sample that leads to the formation of an O<sub>2</sub> containing functional group such as hydroxyl, carbonyl, or carboxyl group. The production of these functional groups leads to an increase in wettability and thus increases the effective surface area available for dissolution, which increases the dissolution rate.

#### Liquisolid Compacts

Here, low soluble hydrophobic drugs dissolved in non-volatile, nontoxic, hydrophilic solvents like polyethylene glycol, glycerine, propylene glycol, or polysorbate-80 mixed with carriers like microcrystalline cellulose, lactose, or polyvinyl pyrrolidone- K30 along with coating materials like silica in optimized proportions and finally compressed into a compact mass. The increased bioavailability is due to either increased surface area of drug available for release, an increased aqueous solubility of the drug, or improved wettability of the drug particles.

#### Self-Emulsification

In the absence of external phase (water), the mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvents and co-solvent forms a transparent isotropic solution that is known as the self-emulsifying drug delivery system (SEDDS) and is used for improving lipophilic drug dissolution and absorption. The self-emulsification process is specific to the nature of the oil/surfactant pair, surfactant concentration, oil/surfactant ratio and temperature at which self emulsification occurs.

#### Supercritical fluid technology

A supercritical fluid is a substance at a temperature and pressure above its critical point where distinct liquid and gas phases do not exist. Novel nanosizing and solubilization technology whose application has increased particle size reduction via supercritical fluid (SCF) processes. Generally supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature and critical pressure. SCF processing for micronized particles are rapid expansion of supercritical solutions (RESS) and gas anti-solvents recrystallisation (GAS).

### Rapid expansion of supercritical solutions (RESS)

It is dissolved in a supercritical fluid (such as supercritical methanol) and then through a small nozzle, the solution is rapidly expanded into a region lower pressure and thus the solvent power of supercritical fluids decreases and the solute eventually precipitates. This technique is basically solvent free, so this is a clean technique.

### Gas anti-solvents recrystallization (GAS)

A liquid solvent is required in the process of GAS to dissolve the solute to be micronized; at the process conditions, because the solute is insoluble in the supercritical fluid, the liquid solvent should be completely miscible with the supercritical fluid. The extract of the liquid solvent by supercritical fluid leads to the instantaneous precipitation of the solute.

### Lipid based delivery system/Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are particulate systems with mean particle diameters ranging from 50-1000 nm and they are derived in oil in water emulsions by replacing liquid lipid by solid lipid.

### Micro-emulsion Technology

A micro-emulsion is a four component system composed of external phase, internal phase, surfactant and co-surfactant. It is a dispersion made of water, oil, and surfactant(s) that is an isotropic and thermodynamically stable system of two immiscible liquids stabilized by interfacial films of surface active molecules with dispersed domain diameter varying approximately from 1 to 100 nm.

### Solid dispersion system

Solid dispersion as a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.

### Vesicular approaches

#### Liposomes

Liposomes are microscopic, synthetic cells used as sustained-action delivery vehicles for a wide variety of drugs, vaccines, enzymes, non-enzyme proteins, and genetic material and now for some nutritional supplements as well. Liposomes with defined particle size and instantaneous loading procedures with poorly water soluble drugs liposomes are certainly useful options to increase the solubility of poorly water soluble compounds offer a dynamic and adaptive technology for enhancing drug solubility.

#### Niosomes

Niosomes are a novel drug delivery system in which the medication is encapsulated in a vesicle. The vesicle is composed of a bilayer of non-ionic surface active agents and hence the name niosomes.

#### Pharmacosomes

Pharmacosomes are colloidal, Nano metric size micelles, vesicles or may be in the form of hexagonal assembly of colloidal drug dispersions attached covalently to the phospholipid. Pharmacosomes act as befitting carrier for delivery of drugs quite precisely owing to their unique properties like small size, amphiphilicity, active drug loading, high entrapment efficiency, and stability. Generally any drug containing an active hydrogen atom (-NH<sub>2</sub>, -COOH, -OH etc.) can be esterified to the lipid with or without spacer chain that strongly result in an amphiphilic compound which will make possible membrane tissue or cell wall transfer in the organism.

### CONCLUSION

Solubility is the most important physical characteristic of a drug for its oral bioavailability, formulation, development of different dosage form of different drugs, therapeutic efficacy of the drug and for quantitative analysis. Proper selection of solubility enhancement method is the key to ensure the goals of a good formulation.

### REFERENCES

1. Bajaj H, Bisht S, Yadav M, Singh V (2011). Bioavailability enhancement: a review. *International Journal of Pharma and Bio Sciences* 2(2):202-216.
2. Kumar S, Singh P (2016). Various techniques for solubility enhancement: An overview. *The Pharma Innovation Journal* 5(1):23-28.
3. Hetal T, Bindesh P, Sneha T (2010). A review on techniques for oral bioavailability enhancement of drugs. *International Journal of Pharmaceutical Sciences Review and Research* 4(3); 203-223
4. Patil MS Sheetal Z, Godse ZS, Saudagar RB (2013). Solubility enhancement by various techniques: an Overview. *World journal of pharmacy and pharmaceutical sciences* 2(6):4558-4572.
5. Singh N, Allawadi D, Singh S, Arora SS (2013). Techniques for Bioavailability Enhancement of BCS Class II Drugs: A Review. *International Journal of Pharmaceutical and Chemical Sciences* 2(2):1092-1101.
6. Sharma D, Soni M, Kumar S, Gupta GD (2009). Solubility Enhancement-Eminent Role in Poorly Soluble Drugs. *Research Journal of Pharmacy and Technology* 2(2):220-224.
7. Nikam SP (2011). A Review: Increasing Solubility of Poorly Soluble Drugs by Solid Dispersion Technique. *Research Journal of Pharmacy and Technology* 4(12):1933-1940.
8. Vadlamudi MK, Dhanaraj S (2016). Disparate practical way of doing solubility enhancement study to improve the bioavailability of poorly soluble drugs. *Journal of Chemical and Pharmaceutical Research* 8(1):208-235.
9. Pardhi D, Shivhare U, Suruse P, Chabra G (2010). Lquisolid Technique For Solubility Enhancement of Poorly Water Soluble Drugs. *Research Journal Pharmaceutical Dosage Forms and Technology* 2(5):314-322.
10. Lachman L, Lieberman HA (2009). *The Theory and Practice of Industrial Pharmacy*, CBS Publication & Distributors Pvt. Ltd. Special Indian Edition 221.
11. Pawar AR, Choudhari PD (2012). Novel Techniques for Solubility, Dissolution Rate and Bioavailability Enhancement of Class II & IV drugs. *Asian Journal of Biomedical & Pharmaceutical Science* 13: 9-14.
12. Varshney HM, Chatterjee A (2012). Solubility Enhancement of Poorly Hydrophilic Drugs by Using Different Newer Techniques: A Review. *International Journal of Therapeutic Applications* 6:8-13.
13. Mukhija U, Soni N, Chawla A, Bhatt DC (2012). Physical Properties and Dissolution Behaviour of Meloxicam/Poloxamer Solid Dispersions Prepared By Hot Melt Method and Microwave Assisted Method. *International Journal of Research In Pharmacy and Science* 2:64-74.
14. Kumar A, Sahoo SK, Padhe K, Kochar PPS, Satpathy A, Pathak N (2011). Review on solubility enhancement techniques for hydrophobic drugs. *Pharmacie Globale International Journal Of Comprehensive Pharmacy* 2(3): 1-7.
15. Vemula VR, Lagishetty V, Lingala S (2010). Solubility enhancement techniques. *International Journal of Pharmaceutical Sciences Review and Research* 1:41-51.
16. Sajid MA, Choudhary V (2012). Solubility enhancement methods with importance of hydrotropy. *Journal of Drug Delivery and Therapeutics* 6:96-101.
17. Patil JS, Kadam DV, Marapur SC, Kamalapur MV (2010). Inclusion Complex System; A Novel Technique to improve the solubility and bioavailability of poorly soluble drugs: A Review. *International Journal of Pharmaceutical Sciences Review and Research* 2(2):29-34.

18. Sareen S, Mathew G, Joseph L (2012). Improvement in solubility of poor water-soluble drugs by solid dispersion. *International Journal of Pharmaceutical Investigation* 2(1):12-17.
19. Mohanachandran PS, Sindhumol PG, Kiran TS (2010). Enhancement of solubility and dissolution rate: An Overview. *Pharmacie Globale International Journal of Comprehensive Pharmacy* 1(4):1-10.
20. Doijad RC, Pathan AB, Gaikwad SS, Baraskar SS, Pawar NB, Maske VD (2012). Liquisolid: A novel technique for dissolution enhancement of poorly soluble drugs. *Current Pharma Research* 3(1):735-749.
21. Chaudhary A, Nagaich U, Gulati N, Sharma VK, Khosa RL (2012). Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modification: A recent review. *Journal of Advanced Pharmacy Education and Research* 2(1):32-67.
22. Thorat YS, Gonjari ID, Homani AH (2011). Solubility enhancement techniques: A Review on conventional and novel approaches. *International Journal of Pharmaceutical Sciences and Research* 2(10):2501-2513.
23. Hu J, Johnston KP, Williams III RO (2004). Rapid dissolving high potency danazol powders produced by spray freezing into liquid process. *Int. J. Pharm.* 271: 145-154.
24. Lipinski C (2002). Poor aqueous solubility – an industry wide problem in drug delivery. *Am. Pharm. Rev.* 5:82-85.
25. Chauhan NN, Patel NV, Suthar SJ, Patel JK, Patel MP (2012). Micronization of BCS-II Drugs by various approaches for solubility enhancement-A Review. *Research Journal of Pharmacy and Technology* 5(8):999-1005.