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SOLUBILITY- A COMPLETE AND DETAILED REVIEW

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ABSTRACT

For achieving maximum therapeutic effect or action of drug in human body, drug must be bioavailable, which depends on solubility and Pka of drug. The drugs which are poorly water soluble or insoluble produce various side effects such as gastric irritation, stomach pain, peptic and esophageal ulcer etc. A new drug must be soluble as well as permeable to various tissue or organ. Whereas only 9% of new drug candidates have both the characteristics of high solubility and permeability. The solubility behavior of drug is the major challenge for a formulation scientist in the development of new drug. For BCS class II drugs, enhancement of solubility is important parameter before formulation into dosage form. The aim of this review is to improve the solubility, permeability and bioavailability of poorly soluble drugs by using various different techniques.

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INTRODUCTION

More than 40% of the new chemical entities being generated through drug discovery programmes are poorly water□soluble or lipophilic compounds. Formulating a poorly water soluble drug has always been a challenging problem confronted by the pharmaceutical scientist. An important physicochemical property of a drug substance is solubility, especially aqueous system solubility. A drug must possess some aqueous solubility for therapeutic efficacy. For a drug to enter the systemic circulation and exert a therapeutic effect, it must first be in solution. If the solubility of the drug substance is less than desirable, consideration must be given to improve its solubility. The methods depend on the chemical nature and the type of drug product. Chemical modification of the drug into salt or ester forms is frequently used to increase solubility. A drug's solubility is usually determined by the equilibrium solubility method, by which an excess of the drug is placed in a solvent and shaken at a constant temperature over a long period until equilibrium is obtained.[1] When solid is brought into contact with a liquid, molecules of the former are removed from its surface until equilibrium is established between the molecules.

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The resulting solution is said to be saturated at the temperature of the experiment, and the extent to which the solute dissolves is referred to as its solubility. The extent of solubility of different substances varies from almost imperceptible amounts to relatively large quantities, but for any given solute the solubility has a constant value at a given constant temperature. Under certain conditions it is possible to prepare a solution containing a larger amount of solute than is necessary to form a saturated solution. This may occur when a solution is saturated at one temperature, the excess of solid solute is then removed, and the solution cooled. The solute present in solution, even though it may be less soluble at the lower temperature, does not always separate from the solution, and there is produced a supersaturated solution. Such solutions, formed by sodium thiosulfate or potassium acetate, for example, may be made to deposit their excess of solute by vigorous shaking, scratching the side of the vessel in contact with the solution, or introducing into the solution a small crystal of the solute. Supersaturated solutions are considered to be thermodynamically unstable systems and, therefore, usually return to a saturated solution by excluding the excess solute. [2] Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature and in qualitative terms, it may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion [3].The solubility of a drug may be

expressed as parts, percentage, molarity, molality, volume fraction, and mole fraction. Solubility is generally defined as the concentration of the compound in a solution which is in contact with an excess amount of the solid compound when the concentration and the solid form do not change over time[4,5,6]. Compounds with solubility below 0.1 mg/ml face significant solubilization obstacles and are considered practically insoluble drugs according to United States Pharmacopeia (USP) and British Pharmacopoeia (BP). The new drug entities with poor aqueous solubility are becoming more prevalent as result of high-throughput screening in drug discovery. Poor aqueous solubility presents significant challenges, as it reduces the oral absorption and bioavailability [7]. Nevertheless, the required solubility to achieve a good bioavailability must be evaluated in view of both the dose and the permeability. Maximum absorbable dose (MAD) "derived by Johnson and Swindell, 1996 and later by Curatolo, 1998" presents the required solubility and permeability needed to achieve a good oral absorption. Incomplete absorption should be expected if the dose is higher than the MAD value:

MAD = Cs . ka . SIWV. SITT

Where Cs is the solubility (mg/ml) at pH 6.5; ka is the intestinal absorption rate constant (min-1); SIWV is the fluid volume in the small intestine (ml); and SITT the small intestinal transit time (min). Solubility, dose and permeability are also the key underlying parameters in Biopharmaceutical classification system (BCS) which groups poorly soluble drugs as class II (poorly soluble and highly permeable) and class IV (poorly soluble and poorly permeable). Drug substances are considered as highly soluble, if the largest strength is soluble in ≤250mL over the physiological pH range from 1.0 to 7.5. Otherwise, the drug substance is considered to be poorly soluble. The highly permeable compounds are defined as those compounds that demonstrate >90 % absorption of the administered dose. Otherwise, the drug substance is considered to be poorly permeable [9,10,11]. A further model generates three dimensionless numbers; dose number (D_0), dissolution number (D_n) and absorption number (A_n) for assessment of whether dissolution rate, solubility and/or permeability are likely to limit the oral absorption in gastro intestinal tract. In this model the drug considers as dissolution rate-limited absorption if the drug particles cannot dissolve completely during the transition time to the absorption site, whereby increasing the dose and/or reducing the particle size to sub-micron range should enhance the absorption. On the other hand if the amount of fluid available in gastrointestinal tract is not enough to dissolve the administered dose, the solubility becomes the rate limiting step in absorption. In the case of permeability-limited absorption, the transition rate of the drug across the gut wall is too slow during the residence time in the absorption [11,12,13].

Basic factors affecting dissolution rate: Several factors affecting the rate at which the solid dissolves in the solvent are described in Noyes Whitney equation (Noyes and Whitney, 1897):

$$\boldsymbol{dc_x/d_t = D.A/h\ (c_s - c)}$$

Where, $dcxdt$ gives the dissolution rate and is a function of diffusion coefficient of the solute in solution (D), the surface area of the exposed compound (A), the thickness of the diffusion layer (h), the saturation concentration of the compound in the diffusion layer (CS) and the concentration in the well-stirred bulk (C). Diffusion coefficient is constant and cannot be significant altered by modifying the drug structure. Furthermore, changing the agitation speed can alter the thickness of diffusion layer in-vitro but it is not applicable in-vivo. Therefore, improving solubility and increasing surface area of the compounds are the only available variables to enhance the in-vivo dissolution rate of poorly soluble drugs [6]. Drug solubility is the maximum concentration of the drug solute dissolved in the solvent under specific condition of temperature, pH and pressure. 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 [14]. The solubility of a drug is described in various descriptive terms which is based on the amount of drug dissolved in solvent and discussed in Table-1.

Table 1. Definitions of Solubility

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

Methods of Expressing Solubility [2]

When quantitative data are available, solubility may be expressed in several ways. For example, the solubility of sodium chloride in water at 25°C may be stated as, 1 g of sodium chloride dissolves in 2.786 mL of water. (An approximation of this method is used by the USP.) 35.89 g of sodium chloride dissolves in 100 mL of water. 100 mL of a saturated solution of sodium chloride in water contains 31.71 g of solute. 100 g of a saturated solution of sodium chloride in water contains 26.47 g of solute. 1 L of a saturated solution of sodium chloride in water contains 5.425 moles of solute. This also may be stated as a saturated solution of sodium chloride in water is 5.425 molar with respect to the solute. In order to calculate item 3 above from items 1 or 2, it is necessary to know the density of the solution, which in this case is 1.198 g/mL. To calculate item 5, the number of grams of solute in 1000 mL of solution (obtained by multiplying the data in item 3 by 10) is divided by the molecular weight of sodium chloride, namely 58.45.

Several other concentration expressions are also available. Molality is the number of moles of solute in 1000 g of solvent and could be calculated from the data in item 4 by subtracting grams of solute from grams of solution to obtain grams of solvent, relating this to 1000 g of solvent and dividing by molecular weight to obtain moles. Mole fraction is the number of moles of a component divided by total number of moles in that solution. Mole percent may be obtained by multiplying mole fraction by 100. Normality refers to the number of gram equivalent weights of solute dissolved in 1000 mL of solution. In pharmacy, use also is made of three other concentration expressions. Percent by weight (% *w/w*) is the number of grams of solute per 100 g of solution and is exemplified by item 4 above. Percent weight in volume (% *w/v*) is the number of grams of solute per 100 mL of solution and is exemplified

by item 3 above. Percent by volume (% *v/v*) is the number of milliliters of solute in 100 mL of solution, referring to solutions of liquids in liquids. The USP indicates that the term percent, when unqualified, means percent weight in volume for solutions of solids in liquids and percent by volume for solutions of liquids in liquids. In pharmacopeial texts, when it has not been possible, or in some instances not desirable, to indicate exact solubility, a descriptive term is used. Table-1 indicates the usual meaning of such terms.

Process of solubilisation [15]

The process of solubilisation 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 solvent and the solute molecule or ion. When Solubilisation process occur break down of solute bond occurs and holes can be seen as shown in Figure 1. When solubilisation process occur solid molecules break down because of breaking of inter molecular bonding shown in Figure 2.About freed solid molecule is integrated in the solvent shown in Figure 3.

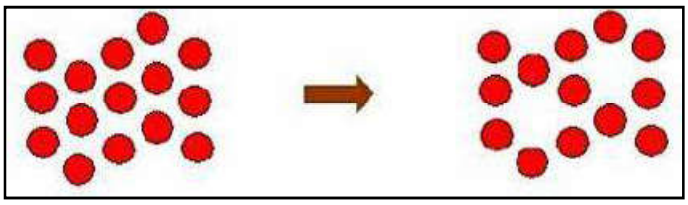


Fig. 1. Holes opens in the solvent

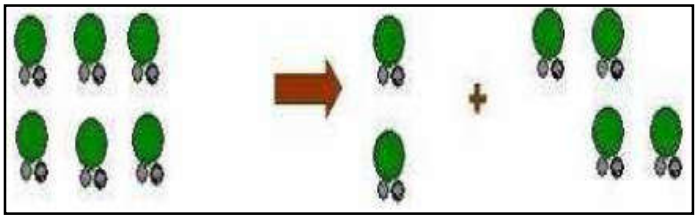


Fig. 2. Molecules of the solid breaks away from the Bulk

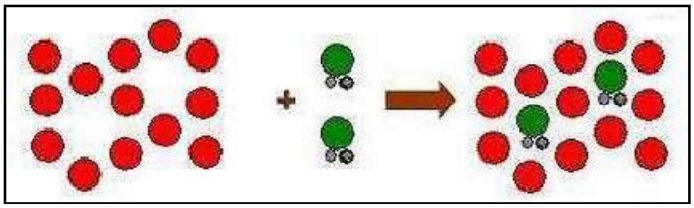


Fig. 3. The freed solid molecule is integrated into the hole in the solvent

Factors Affecting Solubilization [15]

Particle size: The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent. The effect of particle size on solubility can be explained as per the following equation.

$$\log \frac{S}{S_0} = \frac{2 \gamma V}{2.303 R T r}$$

Where,
S is the solubility of infinitely large particles, S is the solubility of fine particles, V is molar volume, *G* is the surface tension of the solid, R is the radius of the fine particle.

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. Generally, an increase in the temperature of the solution increases the solubility of a solid solute. A few solid solutes are less soluble in warm solutions. For all gases, solubility decreases as the temperature of the solution increases.

Pressure: For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure have practically no effect on solubility.

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, 200 grams of zinc chloride can be dissolved. The great difference in the solubilities of these two substances is the result of differences in their nature.

Molecular size: The larger the molecule or the higher its molecular weight the less soluble the substance. Larger molecules are more difficult to surround with solvent molecules in order to solvate the substance. In the case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent.

Polarity: Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute 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 negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction.

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.

Need of Solubility [16]

Drug absorption from the GI tract can be limited by a variety of factors most significant contributor being poor aqueous solubility and poor membrane permeability of the drug molecule. When administered an active agent orally it must first dissolve in gastric and/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. 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 absorption, so increasing the solubility in turn increase the bioavailability for BCS class

II & IV drugs [4]. BCS Classification System with examples of different drug is discussed in Table-2.

Table 2. Biopharmaceutical Classification System [5]

BCS Class I	High Solubility High Permeability	β-blockers propranolol, Metoprolol
BCS Class II	Low Solubility High Permeability	NSAID's Ketoprofen, Antiepileptic Carbazepine
BCS Class III	High Solubility Low Permeability	β blockers Atenolol,H_2 antagonist Ranitidine
BCS Class IV	Low Solubility Low Permeability	Diuretics Hydrochlorothiazide

Techniques for solubility enhancement: Various techniques have been used in attempt to improve solubility and dissolution rates of poorly water soluble drugs which include as following:

Particle size Reduction [17]: The solubility of drug is often intrinsically related to drug particle size; as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows greater interaction with the solvent which causes an increase in solubility.

Conventional methods: Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. Particle size reduction is thus permitting an efficient, reproducible, and economic means of solubility enhancement. However, the mechanical forces inherent to comminution, such as milling and grinding, often impart significant amounts of physical stress upon the drug product which may induce degradation. The thermal stress which may occur during comminution and spray drying is also a concern when processing thermo sensitive or unstable active compounds.

Micronization: Micronization is technique for the particle size reduction. Micronization increases the dissolution rate of drugs through increased surface area, it does not increase equilibrium solubility. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills and so forth micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug [18]. These processes were applied to griseofulvin, progesterone, spironolactone diosmin, and fenofibrate. For each drug, micronization improved their digestive absorption, and consequently their bioavailability and clinical efficacy. Micronized fenofibrate exhibited more than 10-fold (1.3% to 20%) increase in dissolution in at 30 minutes biorelevant media [19, 20].

Milled Product: It is done by milling techniques using jet mill, rotor stator colloid mills etc. Particle size reduced by milling process which leads to the increase in surface area improves the dissolution properties of the drug. Not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug [21].

Nanonization [22]: Recently, various nanonization strategies have emerged to increase the dissolution rates and bioavailability of numerous drugs that are poorly soluble in water. Nanonization broadly refers to the study and use of materials and structures at the nanoscale level of approximately 100 nm or less. Nanonization can result in improved drug solubility and pharmacokinetics, and it might also decrease systemic side-effects [23]. For many new chemical entities with very low solubility, oral bioavailability enhancement by micronization is not sufficient because micronized product has the tendency to agglomerate, which leads to decrease effective surface area for dissolution, the next step is nanonization. There are different techniques used for nanonization of drug.

Table 3. Current marketed product based on nanocrystal technology [44]

Product	Drug	Company
RAPAMUNE®	Sirolimus	Wyeth
PAXCEED	Paclitaxel	Angiotech
TRIGLIDE™	Fenofibrate	First Horizon Pharmaceutical
TRICOR®	Fenofibrate	Abbott
AVINZA®	Morphine Sulphate	King Pharmaceutical

Nanosuspension is another technique which is sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants. The nanosuspension approach has been employed for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel and bupravaquon. The advantages offered by nanosuspension is increased dissolution rate is due to 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. Nanosuspensions are produced by homogenization, wet milling process and also by other novel approaches [21].

Solubilization By Surfactants [24]: Surfactants are molecules with distinct polar and nonpolar regions. The polar group can be anionic, cationic, zwitterionic or nonionic. When small polar molecules are added they can accumulate in the hydrophobic core of the micelles. This process of solubilization is very significant in industrial and natural processes. The addition of surfactants may decrease the surface tension and increase the solubility of the drug within an organic solvent. The use of surfactants to improve the dissolution performance of poorly soluble drug products is possible. The surfactants are also used to stabilize drug suspensions. When the concentration of surfactants more than their critical micelle concentration (CMC, which is in the range of 0.05–0.10% for most surfactants), micelle formation occurs which entrap the drugs within the micelles. This is known as micellization and generally results in enhanced solubility of poorly soluble drugs.

Cosolvency [25] : The solubility of poorly soluble drugs in water can be increased by mixing it with some water miscible solvent in which the drug is readily soluble. This process is known as cosolvency and the solvent used in combination are known as cosolvent. Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly known as solvent blending. There is a dramatic change in the solubility of drugs by addition of organic co-solvent into the water. The cosolvents are having hydrogen acceptor or donor groups with a small hydrocarbon region. The hydrophobic hydrocarbon region usually interferes with the hydrogen bonding network of water which consequently reduces the intermolecular attraction of water while the hydrophilic hydrogen bonds ensures water solubility.

Hydrotropy: Hydrotrophy is a solubilisation process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute.

Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water-soluble drugs [21]. 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 result in "salting in" of non electrolytes called "hydrotropic salts" a phenomenon known as "hydrotropism"[26]. Hydrotropic solutions do not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute. 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[27, 28].

Table 4. Agents used for hydrotropic solubilisation of drugs [22]

Drug	Additive used to exhibit hydrotropism
Cefadroxil	Potassium acetate, potassium citrate
Paracetamol	Sodium acetate, Urea
Theophylline	Sodium salicylate
Nifedepine	Sodium salicylate
Ketoprofen	Urea, sodium citrate

The hydrotropes are known to self-assemble in solution. 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 dodecylated oxidibenzene [29].The aromatic hydrotropes with anionic head groups are mostly studied compounds. They are large in number because of isomerism and their effective hydrotropeaction may be due to the availability of interactive piorbitals. Hydrotropes with cationic hydrophilic group are rare, e.g. salts of aromatic amines, such as procaine hydrochloride. Besides enhancing the solubilisation of compounds in water, they are known to exhibit influences on surfactant aggregation leading to micelle formation, phase manifestation of multicomponent systems with reference to nanodispersions 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 [30].

P^H Adjustment [31] : Poor water soluble drug may potentially dissolve in water by applying a pH change. To access the solubility of this approach, the buffer capacity and tolerability of the selected pH are important to consider. Solubilized excipients that increase environmental pH within the dosage form to a range higher than pKa of weekly acidic drugs increase the solubility of that drug, those excipients that act as alkalizing agents may increase the solubility of weekly basic drugs.

Sonocrystallisation [32]**:** 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.

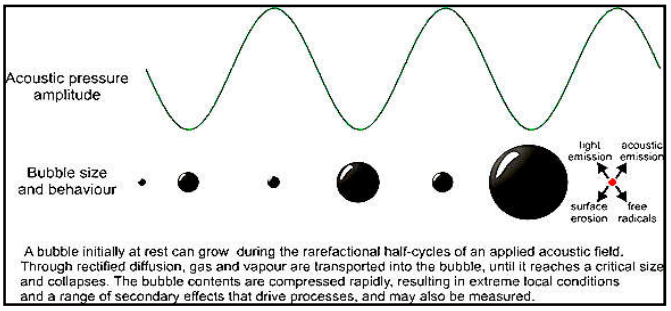


Figure 4. Sonocrystallisation process

Supercritical Fluid (scf) Process [33]: The number of applications and technologies involving 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 (temperature and pressure) make SCFs attractive for pharmaceutical research [34]. A SCF exists as a single phase above its critical temperature (Tc) and pressure (Pc). SCFs have properties useful to product processing because they are intermediate between those of pure liquid and gas (i.e., liquid-like density, gas-like compressibility and viscosity and higher diffusivity than liquids). 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 [35, 36]. 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 nano suspensions of particles 5-2,000 nm 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 [37, 38]. 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) [39, 40].

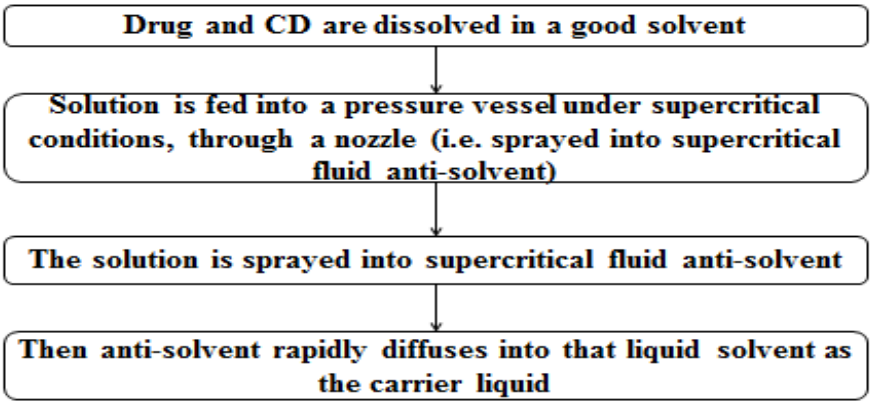


Table 5. Supercritical fluid along with their properties. [21]

Solvent	Molecular Weight (g/mol)	Critical Temperature (k)	Critical Pressure [MPa (atm)]	Density (g/cm)
Carbon dioxide	44.01	304.1	7.38(72.8)	0.469
Water	18.02	647.3	22.12(218.3)	0.348
Methane	16.04	190.4	4.60(45.4)	0.162
Ethane	30.07	305.3	4.87(48.1)	0.203
Propane	44.09	369.8	4.25(41.9)	0.217
Ethylene	28.05	282.4	5.04(49.7)	0.215
Propylene	42.08	364.9	4.60(45.4)	0.232
Methanol	32.04	512.6	8.09(79.8)	0.272

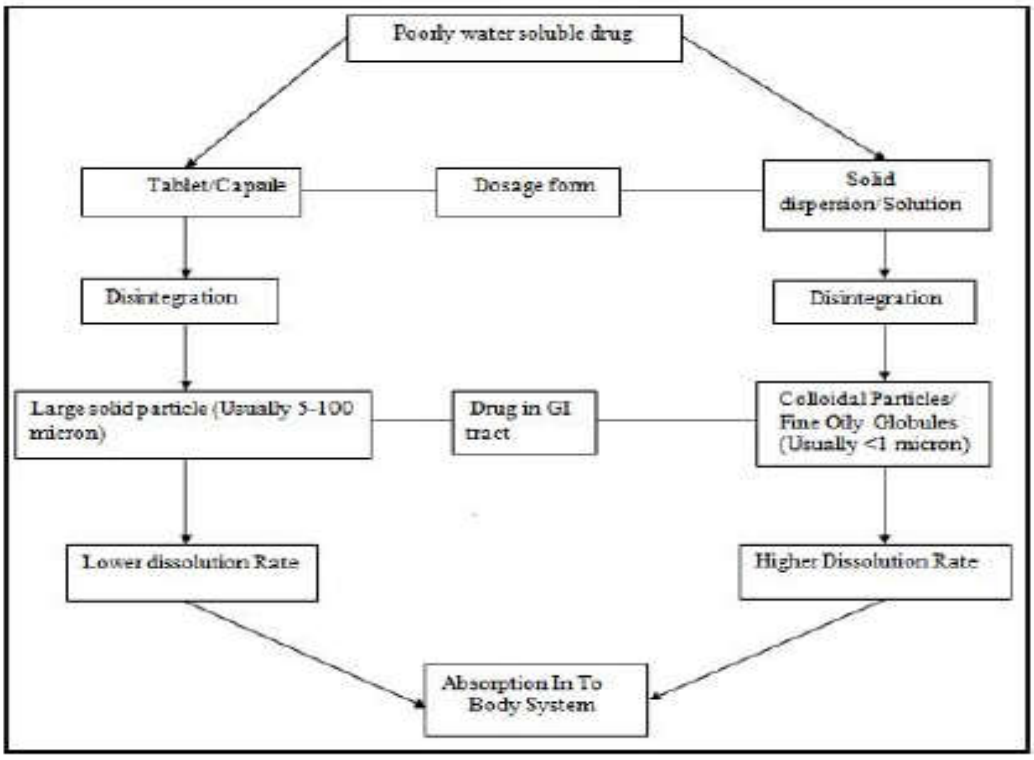


Figure 5. A Schematic representation of the bioavailability of poorly soluble drugs by solid dispersion compared with conventional tablets or capsules [22]

Solid Dispersion: Solid dispersion as 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 isolated molecularly, in amorphous particles or in crystalline particles. Solid dispersion can also be referred as the dispersion of one or more active ingredients in an inert matrix at solid state prepared by the melting, solvent, and melting solvent method [20]. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols, Plasdone-S630. Many times surfactants may also used in the formation of solid dispersion. Surfactants like Tween-

80, Docusate sodium, Myrj-52, Pluronic-F68 and Sodium Lauryl Sulphate are used [41].

Techniques of Solid Dispersion [42]

The fusion (melt) method: Accurately weighed amounts of carrier(s) are placed in an aluminum pan on a hot plate and liquefy, with constant stirring, at a temperature of about 60°C. An accurately weighed amount of active drug is incorporated into the melted carrier(s) with stirring to ensure homogeneity. The mixture is heated until a clear homogeneous melt is obtained. The pan is then removed from the hot plate and allowed to cool at room temperature.

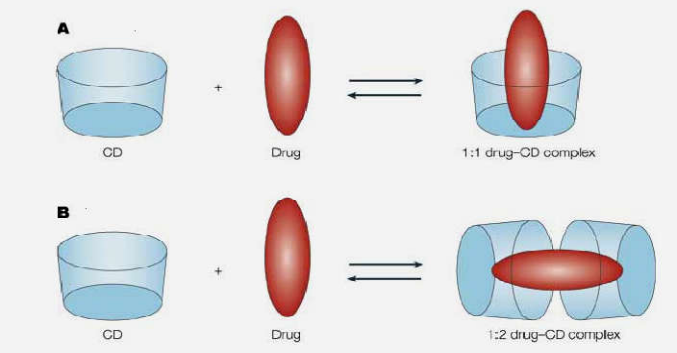
The solvent method: Accurately weighed amounts of active drug and carrier(s) are dissolved in minimum quantities of chloroform in a round-bottom flask. The solvent is removed using a rotary evaporator. The obtained solid dispersion is transferred on to the aluminum pan and allowed to dry at room temperature.

Dropping method: A solid dispersion of a melted drug-carrier mixture is pipetted and then dropped onto a plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. Because viscosity is highly temperature dependent, it is very important to adjust the temperature so that when the melt is dropped onto the plate it solidifies to a spherical shape [8]. Solid dispersion of griseofulvin and polyethylene glycol 8000 (Gris-PEG®) is commercially available.

Table 5. Carriers for solid dispersions [58]

Chemical Class	Examples
Acids	Citric acid, Tartaric acid
Sugars	Dextrose, Sucrose, Sorbitol
Polymeric Materials	Polyvinylpyrrolidone, PEG-4000,Cellulose
Surfactants	Polyxyethylene Stearate, Tweens and Spans
Miscellaneous	Urea, Urethase

Complexation [43]: In complexation technique,the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host).

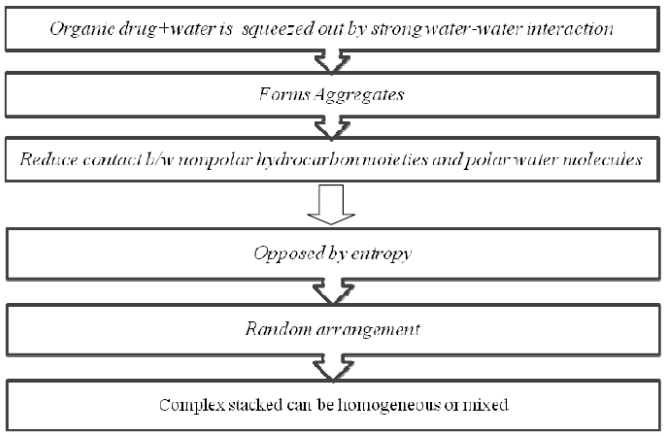


Advantages

- Good enhancement in solubility
- Use of conventional equipment.

Inclusion complexes include the use of hydrophilic polymers which on contact with the medium dissolve rapidly, resulting in the fine precipitation of the drug.

Self association and stacking complexation



Solid inclusion complexes

Kneading Technique: In this technique, cyclodextrin (CD) is impregnated with water and converted to paste. Drug is then added and kneaded for specified time. The kneaded mixture is then dried and passed through sieve if required.

Co-precipitation: Required amount of drug is added to the solution of β-CD. The system is kept under magnetic agitation with controlled process parameters and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex.

Neutralization: Drug is added in alkaline solution like sodium hydroxide, ammonium hydroxide. A solution of β-Cyclodextrin is then added to dissolve the joined drug. The clear solution obtained after few seconds under agitation is neutralized using HCl solution until reaching the equivalence point. At this moment, the appearance of a white precipitate could be appreciated, corresponding to the formation of the inclusion compound. The precipitate is then filtered and dried.

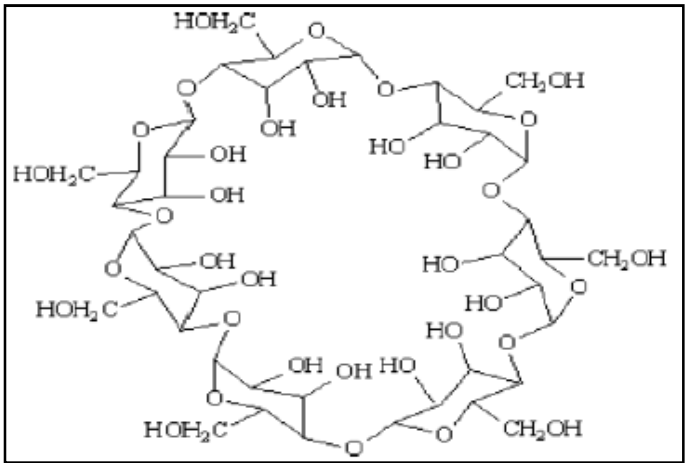
Co-grinding: Drug and cyclodextrin are mixed and the physical mixture is introduced in a suitable mill like oscillatory mill and grinded for suitable time.

Spray-Drying Method: Drug is dissolved in suitable solvent and the required stoichiometric amount of carrier material like β-cyclodextrin is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is then spray dried.

Microwave Irradiation Method: This technique involves the microwave irradiation reaction between drug and complexing agent using a microwave oven. The drug and CD in definite molar ratio are dissolved in a mixture of water and organic solvent in a specified proportion into a round b flask. The mixture is reacted for short time of about one to two minutes at 60 °C in the microwave oven. After the reaction completes, adequate amount of solvent mixture is added to the above reaction mixture to remove the residual, uncomplexed free drug and CD. The precipitate so obtained is separated using whatman filter paper, and dried in vacuum oven at 40 °C for 48 hrs.

Cyclodextrins: Cyclodextrins are macrocyclic torus shaped molecules formed by D-(+)-glucopyranose units. Size and

shape of cyclodextrin is correlated to the type and number of (1,4) linkages between those units. Three naturally occurring cyclodextrins are α-Cyclodextrin, β-Cyclodextrin, and γ-Cyclodextrinare those with 6,7and 8of these units respectively. Cyclodextrins consist of glucose monomers arranged in a donut shape ring.Molecular formula $(C_6H_{10}O_5)_7$



Cyclodextrins are sparingly soluble in water; freely soluble in hot water; slightly soluble in ethanol. The complexation with cyclodextrins is used for enhancement of solubility. The enzymatic degradation of starch by cyclodextrin-glycosyltransferase (CGT) produces cyclic oligomers, Cyclodextrins. Cyclodextrin inclusion is a molecular phenomenon in which usually only one guest molecule interacts with the cavity of a cyclodextrin molecule to become entrapped and form a stable association. The internal surface of cavity is hydrophobic and external is hydrophilic; this is due to the arrangement of hydroxyl group within the molecule. Molecules or functional groups of molecules those are less hydrophilic than water, can be included in the cyclodextrin cavity in the presence of water. In order to become complex, the "guest molecules" should fit into the cyclodextrin cavity. The cavity sizes as well as possible chemical modifications determine the affinity of cyclodextrins to the various molecules. CDs are capable of forming inclusion complexes with many drugs by taking up a whole drug molecule or some part of it into the cavity. Such molecular encapsulation will affect many of the physicochemical properties of drugs, such as their aqueous solubility and rate of dissolution. The rate and extent of absorption of class IIand class IV compounds is highly dependent on the bioavailability which ultimately depends on solubility. . This is most widely used method to enhance water solubility and increase stability of hydrophobic drugs by using cyclodextrins.

Derivatives of cyclodextrin

RM βCD	Randomly methylated β–CD
HP βCD	Hydroxy propyl β –CD
HP γ-CD	hydroxyl propyl γ-CD
DM β-CD	2,4-dimethyl β –CD
SBE βCD	Sulfobutylether β- CD

The rifampicin-CD inclusion compound can improve the lung transport of drug when nebulized with compatible pulmonary deposition and achieve required concentration of drug in broncho-alveolar epithelium lining-fluid when administered as aerosolized solution. [44]

Table 6. List of complexing agents [59]

Types	Examples
Inorganic	IB-
Coordination	Hexamine, cobalt(III), chloride
Chelates	EDTA, EGTA
Metal-Olefin	Ferrocene
Inclusion	Cyclodextrins, Choleic acid
Molecular Complexes	Polymers

Self-emulsifying or self-micro emulsifying systems [45]: Self-emulsifying or self-micro emulsifying systems use the concept of in-situ formation of emulsion in the gastrointestinal tract. 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)**,** [46] in the absence of external phase (water) and forms fine o/w emulsions or micro-emulsions spontaneously upon dilution by the aqueous phase in the GIT and is used for improving lipophilic drug dissolution and absorption. The ease of emulsification could be associated with the ease of water penetrating into the various liquids crystalline or gel phases formed on the surface of the droplet. One of the advantages of SEDDS in relation to scale up and manufacture is that they form spontaneously upon mixing their components under mild agitation and they are thermodynamically stable. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations. The large quantity of surfactant in selfemulsifying formulations (30-60%) irritates GIT. Most selfemulsifying systems are limited to administration in lipid filled soft or hard shelled gelatin capsules due to the liquid nature of the product. Interaction between the capsule shell and the emulsion should be considered so as to prevent the hygroscopic contents from dehydrating or migrating into the capsule shell [47]. A Neoral-R is an example of self microemulsfying drug delivery system (SMEDDS). Depending on the dose level, the relative bioavailability of cyclosporine-α administered. A Neoral-R could be 174-239% of the bioavailability of cyclosporine-α from Sandimmune-R, the originally marketed formulation. Emulsion droplet size is a major factor influencing bioavailability of drugs from emulsion formulations, with small droplet radii enhancing the plasma levels of drugs, in part due to direct lymphatic uptake. Since SMEDDS contain high concentration of surfactants, they should be limited to oral applications and may not be advisable for long term use due to the potential of causing diarrhea [48].

High Pressure homogenization [49]: Homogenization can be performed in water (Disso cubes) or in non–aqueous media or water reduced media (nanopure). In high pressure homogenization, an aqueous dispersion of the crystalline particles is passed through a narrow homogenization gap with a very high velocity. A heat exchanger should be used when using temperature sensitive materials because high pressure homogenization may cause increase in sample temperature leads to increase solubility.

Liquisolid Techniques [50]: The liquisolid technique is a novel concept where a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material. Once the carrier is saturated with liquid, a liquid layer is formed on

the particle surface which is instantly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing, and compressible powder is obtained.

Neutralization [51]: Drug is added in alkaline solution like sodium hydroxide, ammonium hydroxide. A solution of β-Cyclodextrin is then added to dissolve the joined drug. The clear solution obtained after few seconds under agitation is neutralized using HCl solution until reaching the equivalence point. At this moment, the appearance of a white precipitate could be appreciated, corresponding to the formation of the inclusion compound. The precipitate is then filtered and dried.

Spray drying/atomization [52]: In this method, host solution prepared generally in ethanol: water 50% v/v. To this guest is added and resulting mixture is stirred for 24 hr. at room temperature and solution is spray dried by observing following conditions-air flow rate, atomizing air pressure, inlet temperature, outlet temperature, flow rate of solution etc. Product obtained by passing through 63-160 micrometer granulometric sieve.

Cryogenic Method [53]: Cryogenic techniques have been developed to enhance the dissolution rate of drugs by creating nanostructured amorphous drug particles with high degree of porosity at very low-temperature conditions. Cryogenic inventions can be defined by the type of injection device (capillary, rotary, pneumatic, and ultrasonic nozzle), location of nozzle (above or under the liquid level), and the composition of cryogenic liquid (hydrofluoroalkanes, N2, Ar, O2, and organic solvents). After cryogenic processing, dry powder can be obtained by various drying processes like spray freeze drying, atmospheric freeze drying, vacuum freeze drying, and lyophilisation.

Techniques of Cryogenic Method

Spray Freezing onto Cryogenic Fluids: Briggs and Maxvell invented the process of spray freezing onto cryogenic fluids. In this technique, the drug and the carrier (mannitol, maltose, lactose, inositol, or dextran) were dissolved in water and atomized above the surface of a boiling agitated fluorocarbon refrigerant. Sonication probe can be placed in the stirred refrigerant to enhance the dispersion of the aqueous solution.

Spray Freezing into Cryogenic Liquids (SFL): The SFL particle engineering technology has been used to produce amorphous nanostructured aggregates of drug powder with high surface area and good wettability. It incorporates direct liquid-liquid impingement between the automatized feed solution and cryogenic liquid to provide intense atomization into microdroplets and consequently significantly faster freezing rates. The frozen particles are then lyophilized to obtain dry and free-flowing micronized powders.

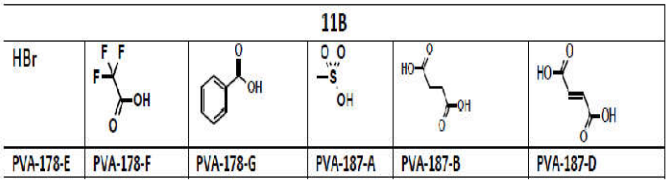
Spray Freezing into Vapor over Liquid (SFV/L): Freezing of drug solutions in cryogenic fluid vapours and subsequent removal of frozen solvent produces fine drug particles with high wettability. During SFV/L the atomized droplets typically start to freeze in the vapor phase before they contact the cryogenic 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.

Ultra-Rapid Freezing (URF): Ultra-rapid freezing is a novel cryogenic technology that creates nanostructured drug particles with greatly enhanced surface area and desired surface morphology by using solid cryogenic substances. Application of drugs solution to the solid surface of cryogenic substrate leads to instantaneous freezing and subsequent lyophilization (for removal of solvent) forms micronized drug powder with improved solubility. Ultra rapid freezing hinders the phase separation and the crystallization of the pharmaceutical ingredients leading to intimately mixed, amorphous drug-carrier solid dispersions, and solid solutions.

Polymeric Alteration [51]: Different crystalline forms of a drug that may have different properties are known as Polymorphs. Polymorphs may differ in physicochemical properties such as physical and chemical stability, shelf-life, melting point, vapor pressure, intrinsic solubility, dissolution rate, morphology, density and biological activities as well as bioavailability. Amongst the stable, unstable and metastable crystalline polymorphs, metastable forms are associated with higher energy with increased surface area, subsequently solubility, bioavailability and efficacy. With regard to bioavailability, it is preferable to change drug from crystal forms into metastable or amorphous forms. However, the possibility of a conversion of the high energy amorphous or metastable polymorph into a low energy crystal form having low solubility cannot be ruled out during manufacture and storage. It is preferable to develop the most thermodynamically stable polymorph of the drug to assure reproducible bioavailability of the product over its shelf-life under a variety of real-world storage conditions.

Salt Formation [31]: Dissolution rate of particular salt is usually different from that of parent compound. Sodium and potassium salt of week acid dissolve more rapidly than that of pure salt. Limitation of salt formation includes epigastric distress due to high alkalinity, reactivity with atmospheric water and carbon dioxide leads to precipitation, patient compliance and commercilation. Example of drugs whose solubility have been increased by salt formation method like Alkali metal salts of acidic drugs like penicillins and strong acid salts of basic drugs like atropine and more water soluble than the parent drug.

Chemical Modifications [54]: Change of pH, use of buffer, derivatization, complexation and Salt formation**.** The salts formation was the approach used in 3D-NET projects to increase the solubility of the target molecules. As a example, the molecule 11B and their salts were evaluated and a different activity was observed related only to their different solubility.



Crystal Engineering [55, 56, 57]: Crystal engineering techniques are developed for the controlled crystallization of drugs to produce high purity powders with well-defined particle size distribution, crystal habit, crystal form (crystalline or amorphous), surface nature, and surface energy . By manipulating the crystallization conditions (use of different solvents or change in the stirring or adding other components to crystallizing drug solution), it is possible to prepare crystals with different packing arrangement; such crystals are called

Table 7. Improved solubility of some drugs

Method	Drugs Example
Micronization	Danazol, carbamazepine, dipyridamole, indomethacin, Cilostazol, ibuprofen, griseofulvin, tipranavir (Aptivus® capsules, Boehringer Ingelheim GmBH), several steroidal and sulfa drugs.
Nanonization	Sirolimus, Paclitaxel, Fenofibrate, Fenofibrate and Morphine Sulphate
High pressure homogenization	Prednisolone, carbamazepine, nifedipine
Cryogenic spraying process	Danazol, carbamazepine, glibenclamide, febantel, itraconazole
Complexation with cyclodextrins	Celecoxib, clotrimazole, bifonazole, praziquantel
Solubilization by surfactants	Spironolactone, Gliclazide, glyburide, glimepiride, glipizide, repaglinide, pioglitazone and rosiglitazone.
Solid dispersion	Griseofulvin, Lurasidone HCL
Cosolvency	Nimodipine IV Injection (Nimotop®, Bayer) and Digoxin Elixir Pediatric (Lanoxin®, GSK)
Hydrotropic solubilisation	Cefadroxil, Theophylline, Nifedepine, Ketoprofen
pH adjustment	Phenytoin Injection
Salt formation	Penicillins, atropine and Morphine
Self microemulsfying drug delivery system (SMEDDS)	Neoral-R

polymorphs. As a result, polymorphs of the same drug may differ in their physicochemical properties such as solubility, dissolution rate, melting point, and stability. Most drugs exhibit structural polymorphism and it is preferable to develop the most thermodynamically stable polymorph of the drug to assure reproducible bioavailability of the product over its shelf-life under a variety of real-world storage conditions.

Conclusion

The basic approaches followed in all the currently used method for solubility enhancement and dissolution enhancement is to maximize the bioavailability and therapeutic efficacy. Proper selection of solubility enhancement method is the key to ensure the goals of a good formulation like good oral bioavailability, better patient compliance and low cost of production. Older methods of solubility enhancement had a problem of irregular shape or size; larger particle size which leads to irregular dissolution, but novel method shown the properties of uniform size which can be used in combination or alone will have potential for the dissolution enhancement of the newer chemical entities. Lipid technology is the latest trend which has affected the Pharma field and is growing by leaps and bounds. Many methods have been patented and future belongs to lipid technology. Dissolution enhancement of poorly water soluble drugs constitute innovative approach which overcome the problem of solubility of dissolution rate limiting step and provide a quick own set of action.

Conflict of Interest: Authors report no conflict of interest.

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