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Review Article

SOLUBILITY AND DISSOLUTION ENHANCEMENT: TECHNOLOGIES AND RESEARCH EMERGED

Kataria Mahesh Kumar[1]*, Bhandari Anil[2]

[1]Research Scholar, Faculty of Pharmaceutical Sciences, Jodhpur National University, Jodhpur (Rajasthan), India

[2]Dean, Faculty of Pharmaceutical Sciences, Jodhpur National University, Jodhpur (Rajasthan), India

***Correspondence**

Kataria Mahesh Kumar

Research Scholar, Faculty of Pharmaceutical Sciences, Jodhpur National University, Jodhpur, India

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Abstract

Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. About 40 % drugs from newly developed chemical entities are lipophilic and fail to reach market due to their poor water solubility. The solubility behavior of drugs remains one of the most challenging aspects in formulation development. The bioavailability of an orally administration drug depends on its solubility in aqueous media over different pH ranges. The insufficient dissolution rate of the drug is the limiting factor in the oral bioavailability of poorly water soluble compounds. Most of drugs are weakly acidic and weakly basic with poor aqueous solubility. Various techniques are used for the improvement of aqueous solubility, dissolution rate and bioavailability of poorly water soluble drugs include micronization, chemical modification, pH adjustment, solid dispersion, nanosuspension, superdisintegrant, liquisolid technique, complexation, co-solvency, micellar solubilization, hydrotrophy etc. The purpose of this review article is to describe the techniques of solubilizaton and research materialized for the attainment of effective absorption and improved bioavailability.

Keywords: Bioavailability, Co-Solvent, Emulsions, Hydrophobic drugs, pH, Micronization, Nanosuspension, Solubility, Solid Dispersion, Solubility Enhancement.

INTRODUCTION

Solubility is defined in quantitative terms as the concentration of solute in a saturated solution at a certain temperature and pressure. Qualitatively it is defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. The United State Pharmacopoeia (USP) and national formulary lists the solubility of drug as the number of milliliters of solvent in which 1 g of solute will dissolve. The Indian pharmacopoeia define the term very soluble, freely soluble, soluble, sparingly soluble, slightly soluble, very slightly soluble and practically insoluble as mentioned in Table 1. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drugs molecules. Solubility is an important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response. Dissolution is defined as the process by which solid substance enters in solvent to yield a solution. The solubility of the drug play prime role in controlling its dissolution from the dosage form. Dissolution of solid dosage forms depends upon the solubility of the drug substance in the surrounding medium. Dissolution is the process in which a solid substance gets dissolve in a given solvent i.e. mass transfer from the solid surface to the liquid phase. A polar solute will dissolve to a greater extent in a polar solvent.

Table: 1 Terms of Solubility

Term[1]	Parts of solvent required for one part of solute
Very soluble	Less than 1 part
Freely soluble	1 to 10 parts
Soluble	10 to 30 parts
Sparingly soluble	30 to 100 parts
Slightly soluble	100 to 1000 parts
Very slightly soluble	1000to 10000 parts
Practically insoluble	More than 10000 parts

Biopharmaceutics Classification System (BCS) is a fundamental guideline associated with the drug dissolution and absorption model, identifies the key parameters controlling the drug absorption and bioavailability and classified the drugs in four classes based on its solubility and intestinal permeability as per Table 2.

Table 2: The Biopharmaceutics Classification System

Class[2,3]	Solubility	Permeability	Characteristics features	Drugs
I	High	High	Well absorption orally	Diltiazem, Atropine, Propanolol, Caffine etc.
II	Low	High	Variable absorption due to solubility limitation	Diclofenac, Itraconazole, Nifedipine, Phenytoin etc.
III	High	Low	Variable absorption due to permeability limitation	Atenolol, Neomycin, Ciprofloxacin, insulin etc.
IV	Low	Low	Meager absorbed due to both solubility and permeability limitations	Furosemide, Methotraxate, Mebendazole, Chlorthiazide etc.

Solubility Enhancement

In general physical methods to improve the dissolution rate can be derived from the equation by Noyes and Whitney;

$$\frac{dc}{dt} = \frac{A \cdot D \cdot (c_s - c_t)}{V \cdot h}$$

Equation 1

dc /dt is the dissolution rate, A denotes surface area, D is the diffusion coefficient of the compound, C_S is the solubility of the compound in the dissolution medium, C_t is the concentration of drug in the medium at time t, V is the volume of the medium, and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

According to this equation there are two main probabilities of improving the dissolution rate of a drug by physical effect. First, A can be increased by micronizing the compounds or changing the surface properties, thus, increasing the wettability of the particles. The second method is to increase the apparent Cs by changing to modifications with higher energetic states or by addition of solubility enhancing excipients[4].

Factor Affecting the Solubility:

Solubility can be affected by various factors such as;

- Particle size: The effect of particle size on solubility is given by Kelvin equation

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

Equation 2

Where S =is the solubility of large particles, S_0= is the solubility of fine particles, V is the molar volume, r is the radius of fine particles and y is the surface tension of solid

- Temperature: If the solution process absorbs energy then the solubility increases with rise in temperature. If the solution process releases energy then the solubility will decrease with increasing temperature.
- Pressure: For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. For solids and liquid solutes, a change in pressure practically has no effect on solubility.
- Nature of the solid: Depending upon the internal structure of the solid it may be either crystalline or amorphous. Crystalline structures exhibit low solubility while amorphous forms exhibit high solubility.
- Polymorphism: The order for dissolution of different solid forms of a drug is Amorphous > Meta stable polymorph > Stable polymer[5].

Techniques of Solubility Enhancement[8-10]

• Particle Size Reduction Micronization • Nanosuspension • Salt formation • Precipitation • Use of precipitation inhibitors (PPIS) • Spray freezing into liquid (SFL)	• Evaporative precipitation into aqueous solution (EPAS) • Selective adsorption on insoluble carriers • Solvent deposition • Eutetic mixtures • Modification of the crystal habit • Complexation • Solubilization by surfactants	• Drug dispersion in carriers • Cosolvency • Liquisolid • pH Adjustment • Hydrotrophy • Supercritical fluid process • Superdisintegrants

Particle Size Reduction

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 a greater interaction with the solvent which cause increase in solubility. These processes were applied to griseofulvin, progesterone, spironolactone and fenofibrate. For each drug, micronization improved their digestive absorption and consequently their bioavailability and clinical efficacy.

Micronization

Micronization is a term used to describe size reduction where the resulting particle size is less than 10 microns which is shown in Figure 1. Micronization size reduction involves acceleration of particles so that grinding occurs by particle-to-particle impact or impact against a solid surface. Fluid energy mills are used for micronization because of the high impact velocities possible as results of particle acceleration in a fast gas stream. Dry powder inhalants and injectable compounds benefit from finer and more defined particle size distributions. The micronization can also be made by spiral jet mill and fluidized-bed jet mill[6].

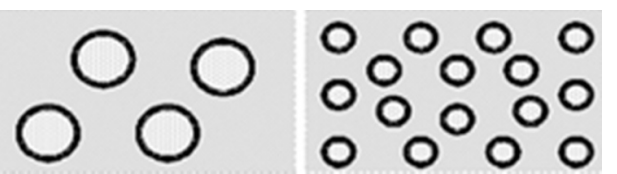

Figure 1: Drug Micronization

Research Materialized in Micronization

The solubility and dissolution was enhanced by micronization techniques for the drug Levonorgestrel, a synthetic progestogen, by Therdana Rao with air jet mill. Micronization enhanced dissolution rate of the drug in 0.1N HCl with 0.1 % sodium lauryl sulphate (SLS) compared to nonmicronized material. The results suggested micronization technique for the preparation of rapidly dissolving formulations of Levonorgestrel, potentially lead to

improvement in the bioavailability of oral Levonorgestrel product[7].

Nanosuspension

Nanosuspensions are submicron colloidal dispersion of pure particles of drug, stabilized by surfactants. The improved 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 consist of the poorly water soluble drug without any matrix material suspended in dispersion. These can be used to enhance the solubility of drugs that are poorly soluble in aqueous as well as lipid media. As a result of increased solubility, the rate of flooding of the active compound increases and the maximum plasma level is reached faster. This is one of the unique advantages that it has over other approaches for enhancing solubility. This approach is useful for molecules with poor solubility, poor permeability or both, which poses a significant challenge for the formulators. The reduced particle size renders the possibility of intravenous administration of poorly soluble drugs without any blockade of the blood capillaries. Nanosuspension can be prepared by precipitation, high pressure homogenization, emulsion and milling techniques. Summary of some techniques is illustrated in Table 3. Mainly there are two methods for preparation of nanosuspensions. The conventional methods of precipitation are called 'Bottom up technology'. The 'Top down Technologies' is the disintegration methods and preferred over the precipitation methods. These include media milling (nanocrystals), high pressure homogenization in water (dissocubes), high pressure homogenization in nonaqueous media (nanopure) and combination of precipitation and high-pressure homogenization (nanoedege)[8].

Table 3: Nanosuspension Formation Technologies

Technology	Merits	Demerits	Drugs Used
Precipitation	Simple, Economical process. Ease of scale up.	Growing of crystals needs to be limit by surfactant addition. Drug must be soluble at least in one solvent.	Carbamazepine, Cyclosporine, Griseofulvin
Emulsion / Microemulsion Template	High drug solubilization. Long shelf life. Ease of manufacture.	Use of high amount of surfactant and stabilizers. Use of hazardous solvent in production.	Breviscapine, Griseofulvin,
High Pressure Homogenizatio n	Applicable to most of the drugs Very dilute as well as highly concentrate. Aseptic production possible.	High number of homogenization cycles. Drug should be in micronized state. Possible contamination from metal ions coming off from the walls.	Albendazole, Aphidicolin, Azithromycin, Fenofibrate
Media Milling	Applicable to the drugs that are poorly soluble in both aqueous and organic media. Little batch to batch variation. High flexibility in handling large quantities of drugs.	Contaminated with materials eroded from balls. Time consuming. Difficult to scale up. Prolonged milling may induce the formation of amorphousand instability.	Cilostazol, Danazol, Naproxen

Research Materialized in Nanosuspensions

- Itoh *et al* reported the colloidal particles formation of many poorly water soluble drugs like griseofulvin, glibenclamide and nifedipine by grinding with polyvinylpyrrolidone and sodium dodecyl sulfate (SDS)[11]
- Muller and Peters 1998 stated that the mean particle size and the span of particle size distribution are two important characteristic parameters because they affect the saturation solubility, dissolution rate, physical stability, even *in vivo* behavior of nanosuspensions[12].
- Bohm 1998 revealed that an inverse relationship exists between the homogenization pressure and the particle size[13].

Salt Formation

Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs[14]. Salts of weak acids and weak bases generally have much higher aqueous solubility than the free acid or base, therefore if the drug can be given as a salt the solubility and dissolution can be improved as with Penicillin V[15]. It is frequently performed on weak acidic or basic drugs because of relatively simple chemical manipulation, which may alter the physicochemical, formulation, biopharmaceutical and therapeutic properties of a drug without modifying the basic chemical structure[16].

Research Materialized in Salt Formation

- Cheong HA *et al* 2002 observed an increase in absorption of piroxicam when formulated as salt formation with Ethanolamines[17].
- Walkling WD *et al* 1983 made an effort to protect xilobam from the effects of high temperatures and high humidity without adversely affecting its dissolution from tablets, by preparing arylsulfonic acid salts and saccharin salt. All of the salts were observed more stable at 74 % relative humidity and 70°C than the free base[18].

Precipitation

In the precipitation method, a dilute solution is first produced by dissolving the substance in a solvent. The solution with the drug is then injected into water, which acts as a bad solvent. At the time of injection, the water has to be stirred efficiently so that the substance will precipitate as nanocrystals. Nanocrystals can be removed from the solution by filtration and then dry in air.

Research Materialized in Precipitation

Cyclosporine dissolved in suitable organic solvent followed by mixing with a non solvent for precipitation of drug in nanosize particle and increased bioavailability was observed[19].

Precipitation Inhibitors (PPIs)

The inclusion of certain polymers within solid dispersion or lipid based formulations can maintain drug super saturation

after dispersion and / or digestion of the vehicle, leading to improvements in bioavailability and variability in exposure. PPIs have broad potential application in the inhibition of drug precipitation in the gastro intestinal tract (GIT). PPIs aim to maintain drug in a supersaturated, thermodynamically unstable state (metastable) over a period of time that is sufficient to allow absorption of drug from GIT. PPIs mode of action is not via co-solvency and they do not typically increase equilibrium drug solubility. Polymers like Hydroxy Propyl Methyl Cellulose (HPMC), Poly Vinyl Propylene (PVP), Poly Vinyl Alcohol (PVA), Poly Ethylene Glycol (PEG) are used as precipitation inhibitors[20].

Research Materialized in (PPIs)

- Liu, 2008 reported that PPIs can act as crystallization inhibitors at both the nucleation and growth (kinetics and crystal habit) stages. Several potential sites of action were identified[21].
- Raghavan *et al*. 2001 revealed that changing the adsorption layer at the crystal solution interface, including the properties of the hydrodynamic boundary layer surrounding the crystal, potentially decreasing the rate of diffusion of drug molecules to the crystal nuclei[20].

Spray Freezing into Liquid (SFL)

Spray freeze-drying is a process in which fine droplets of drug and excipients are sprayed through an ultrasonic nozzle directly into liquid nitrogen which is shown in Figure 2. The frozen droplets are then placed into vials and freeze dried in a standard lyophilizer. They produced spherical particles with diameters from 20 to 90 mm[22].

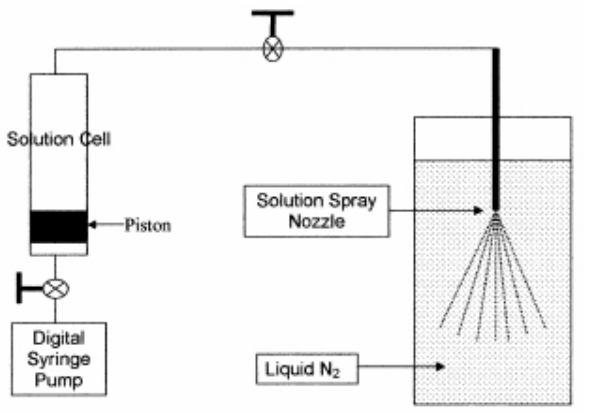

Figure 2: Laboratory Scale SFL Process

Spray freeze drying (SFD) is a feasible method to produce peptide and protein loaded powders for pulmonary and parenteral applications. Different SFD methods have also been developed for powder production. The right choice of the atomization and liquid delivery system has a strong impact on the final product quality[23].

Research Materialized in SFL

- Hu J. *et al* 2003 reported that acetonitrile was an effective alternative solvent for use with the SFL to produce free flowing particles containing carbamazepine with significantly enhanced wetting and dissolution properties[24].
- Engstrom *et al* 2007 observed stable high surface area of lactate dehydrogenase particles produced by spray freezing into liquid nitrogen compared to other techniques[25].
- Rogers TL and Nelsen AC *et al* 2003 observed enhanced dissolution of hydrophobic drug like anazol when formulated by SFL Technique[26,27].
- Vaughn JM *et al* 2005 reported that dissolution rates are faster for the SFL particles as compared to particles formed by evaporative precipitation into aqueous solution technique[28].

Evaporative Precipitation into Aqueous Solution (EPAS)

In the EPAS process (Figure 3) poorly water soluble drug is dissolved in low boiling organic solvents including diethyl ether, methylene chloride, ethyl acetate, dimethyl ether. The solution pumped through a tube where it is heated under pressure to a temperature above the solvent's normal boiling point. The pressure should be sufficient enough to maintain a liquid phase. The solution is sprayed through a fine atomizing nozzle into a heated aqueous solution. The upper temperature limit will depend upon the operating pressure, but is probably low enough so as not to degrade the drug but high enough to evaporate the solvent but not evaporate too much of the water. Rapid evaporation of the organic solvents produces large super saturation of the drugs and rapid precipitation of the drug to produce amorphous particles. A particle stabilizer is added to the organic solution, the aqueous solution or both to optimize particle formation and stabilization. The stabilizers adsorb on to the newly formed drug particle surface, consequently decreasing the surface energy and providing steric and / or electrostatic repulsion between particles. The drug particles are recovered by removing the water from the particles by spray drying, lyophilization, drying with cold air and filtration[29].

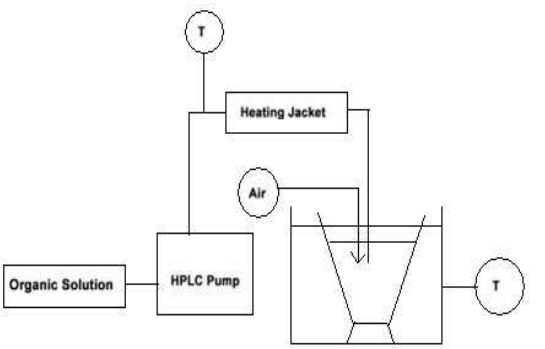

Figure 3: EPAS[30]

Research Materialized in EPAS

- Chen X, *et al*) observed high dissolution rates of danazol with approximately 90 % drug dissolved in 2 minutes[31].
- Sarkari M *et al* 2002 observed enhanced dissolution of poorly water soluble drug carbamazepine due to hydrophilic coating on the particles that enhances wetting, and low crystallinity[32].
- Chen X *et al* 2006 reported that Ketoprofen, a BCS class II drug, dissolves rapidly 98 % in 2 minutes when formulated by EPAS[33].

Selective Adsorption on Insoluble Carriers

A highly active adsorbent such as the inorganic clays bentonite can enhance the dissolution rate of poorly water soluble drugs such as griseofulvin, indomethacin and prednisone by maintaining the concentration gradient at its maximum shown in Figure 4. The basic reasons suggested for the rapid release of drugs from the surface of clays is the weak physical bonding[34].

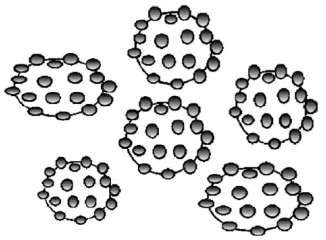

Figure 4: Adsorption of Drug on Insoluble Carrier

Research Materialized in Adsorption on Insoluble Carriers

- Monkhouse DC et al 1972 observed enhanced dissolution rate of indomethacin and probucol when adsorbed on insoluble carrier[35].
- Gupta MK *et al* 2001 concluded that combination of solid dispersion and surface adsorption techniques enhance the dissolution of a poorly water-soluble drug[36].
- Smirnova L *et al* 2004 observed that the release rate of ketoprofen increase in 500 times and that of griseofulvin in 450 times when hydrophilic silica aerogels used as drug carriers[37].
- Williams AC *et al* 2005 reported enhanced dissolution of ibuprofen when microcrystalline cellulose and cross-linked polyvinylpyrrolidone used as carrier[38].
- Srikanth MV *et al* 2010 revealed that the dissolution of bicalutamide enhanced by addition of adsorbents like magnesium aluminum silicate, hydrophilic carrier povidone K30 and combination of both[39].

Solvent Deposition

Solvent deposition method increases the dissolution rate of drug by depositing drug in "minuscular form" on the surface of an adsorbent. The term "minuscular form" implies that the drug has undergone molecular micronization when it is dispersed on the extensive surface of the micro particulate adsorbents. It is an approach used for increasing the dissolution rates of relatively insoluble powders. The solvent deposition system is a solid preparation in which a drug is deposited from a solvent on the surface of a matrix. This step is usually done by simple evaporation of the solvent used for distribution of the drug onto the matrix. This is accomplished by equilibration of the drug in an organic solvent on water-insoluble excipients with an extensive surface e.g., fumed silicon dioxide. During dissolution, since carriers are insoluble, the minuscular drug system releases only free, absorbable drug into solution. Hydrogen bonding and van der Waals' forces are accounted for desorption of the drug from the adsorbent surface. The minuscular drug delivery system can be regarded as drug in a micro-particulate form molecularly dispersed on the very extensive surface of carrier. The resulting decrease in particle size and the concomitant increase in surface area serve to increase the thermodynamic activity of the drug in the dispersed state which, in turn, greatly enhances the rate of solution of the drugt[40].

Research Materialized in Solvent Deposition

Sekiguchi and Obi proposed that the incorporation of a microcrystalline or molecular dispersion of a poorly soluble drug in a solid matrix of water soluble carrier increase the dissolution rate and absorption of the drug[41].

Modification of the Crystal Habit

The manufacturing of a micro crystals implies the creation of additional surface area and hence interface. As the Gibbs free energy change, associated with the formation of additional interface is positive, the micro crystals formed are thermodynamically unstable and tend to minimize their total energy by agglomeration. Kinetically, the process of agglomeration depends on its activation energy. This activation energy can be influenced by adding stabilizers to the system. First requirement for a stabilizing system is that it provides wetting of the hydrophobic surfaces of the drug particles. In recent years, solvent change method (anti solvent precipitation) has been used for micro crystallization of drugs in the presence of excipients for increasing the dissolution rate of poorly water soluble drugs. Powder wettability can be increased through adsorption of hydrophilic stabilizing agent. Precipitation in the presence of stabilizing agent has a positive effect on dissolution rate. This technique is a rapid, easy to handle, needs only common equipment and direct process, which can be performed with ease[42]. Nanocrystals can be produced by bottom up technologies precipitation methods or alternatively by top down technologies (size reduction methods). Co-crystals are more stable, particularly as the co-crystallizing agents are solids at room temperature[43].

Research Materialized in Modification of Crystal Habit

- Tsutsumi S *et al* 2011concluded that co crystals of meconazole show increase in dissolution as compared to its salt formulation[44].
- Chiou WL *et al* 2006 observed an increase in dissolution of chloramphenicol, prednisolone and sulphathiazole when formulated with surfactant treated crystals[45].
- Hickey MB *et al* 2007 revealed that co crystals of carbamazepine are more stable as compared to other formulations[46].

Complexation

Complexation is the association between two or more molecules to form a non bonded entity with a well defined stoichiometry. Complexation relies on relatively weak forces such as london forces, hydrogen bonding and hydrophobic interactions. There are many types of complexation agents. The most common complexing ligands are cyclodextrins, caffeine, urea, polyethylene glycol, N-methyl glucamide. Considerable increase in solubility and dissolution of the drug has been observed by the use of cyclodextrins (CD). Cyclodextrins are non reducing, crystalline, water soluble and cyclic oligosaccharides. Cyclodextrins consist of glucose monomers arranged in a donut-shaped ring. Three naturally occurring cyclodextrins are α-Cyclodextrin, β-Cyclodextrin, and γ- Cyclodextrin[47]. Staching complexes are formed by the overlap of the planar regions of aromatic molecules. Non

polar moieties tend to be squeezed out of water by the strong hydrogen bonding interactions of water. This causes some molecules to minimize the contact with water by aggregation of their hydrocarbon moieties. Some compounds that are known to form staching complexes are as nicotinamide, anthracene, pyrene, methylene blue, benzoic acid, salicylic acid, ferulic acid, gentisic acid, purine, theobromine, caffeine and naphthalene etc. 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 most commonly used host molecules are the cyclodextrins. Complexation of drugs with cyclodextrins enhances aqueous solubility and drug stability. Hydrophilic cyclodextrins are nontoxic in normal doses while lipophilic ones may be toxic; hence, methyl, hydroxypropyl, sulfoalkylated and sulfated derivatives of natural cyclodextrins that possess improved aqueous solubility are preferred for pharmaceutical use[48]. Kneading, Lyophilization / Freeze drying technique, Microwave irradiation method and Supercritical antisolvent technique are based on Inclusion Complex Formation**.**

Research Materialized in Complexation

- Shah SS *et al* 2012 reported that increase in solubility and dissolution rate by Itraconazole - hydroxypropyl β-CD complex (1:2)[49].
- Kata M *et al* 1987 revealed that the β-CD and γ-CD increases the dissolution characteristics and hence the bioavailability of drugs likes furosemide, hydrochlorothiazide, mebendazole, metronidazole, spironolactone, tofisopam[50].
- Ghodke DS *et al* 2010 observed increase in dissolution of domperidone as compared to pure drug and maximum increase was observed in case of inclusion complexes[51].
- Pandit V *et al* 2011 observed greater solubility of pioglitazone with spray dried methyl-β CD complexes (2.29 ± 0.001 mg / ml) in comparison to the kneaded methyl-β CD complexes (1.584 ± 0.053 mg / ml) and pure drug (0.0714 ± 0.0018 mg / ml)[52].

Surfactants

Surfactants are compounds that have molecular structures with two distinct regions i.e. a polar (hydrophilic) head group and a nonpolar (hydrophobic tail). Surfactants can lower surface tension and improve the dissolution of lipophilic drugs in aqueous medium. Surface active agents (surfactants) are substances which at low concentrations, adsorb onto the surfaces or interfaces of a system and alter the surface or interfacial free energy and the surface or interfacial tension. Depending on their charge characteristics the surface active molecules may be anionic, cationic, zwitterionic (ampholytic) or non-ionic. Various surfactants like Polyglycolized glyceride (Labrasol), Tweens, Spans, Polyoxyethylene stearate and synthetic block copolymers viz Poly (propylene oxide)-poly (ethylene oxide), b-poly (ethylene oxide) etc used as carrier for solubility and dissolution enhancement. Improvement of drug solubility by using the amphiphilic surfactants is due to lowering of surface tension between drug and solvent, improvement of wetting characteristics and micellar solubilization of the drugs. To get any substantial solubility enhancement, the surfactant concentration must be at least above the critical micelle concentration (CMC). The CMC will depend upon the surfactant itself and the ionic strength of the media. The amount of surfactant required depends on the CMC and the degree to which the compound partitions into the surfactant micelles[48].

Research Materialized with Surfactants

- Jamzad S *et al* 2006 revealed that solubility of fenofibrate increased directly with addition of Sodium lauryl sulfate as surfactant[53].
- Grace XF *et al* 2012 concluded that poloxamer 407 increases solubility of pioglitazone and glimepiride[54].
- Kadam VD *et al* 2009 revealed that coating of surfactants like PVA, Tween 80 on carvedilol tablet enhances the dissolution with increase in stability[55].

Solid Dispersion

The solid dispersion (SD) approach, to reduce particle size and therefore increase the dissolution rate and absorption of drugs, was first recognized in 1961. The term SD refers to the dispersion of one or more active ingredients in an inert carrier in a solid state. The most commonly used hydrophilic carriers for solid dispersions include poly vinyl pyrrolidone, polyethylene glycols, plasdone-S630. Many times surfactants may also used in the formation of solid dispersion. Surfactants like Tween-80, docusate sodium, Pluronic-F68 and SLS used. Table 4 shows some techniques and material used in formulation of solid dispersion. Some carriers used for solubility enhancement in preparation of solid dispersions are briefly mentioned in Table 5. Table 6 comprises of several marketed drugs designed by solid dispersion.

Methods for Preparation of Solid Dispersion

• Melt / Cool Method:
a. Melting Solvent Method
b. Hot stage extrusion

• Solvent Evaporation:
a. Hot Plate Drying
b. Vacuum drying
c. Slow evaporation at low temperature
d. Rotary evaporation
e. Spray drying
f. Freeze drying
g. Spin drying
h. Fluid bed coating

Table 4: Techniques of Solid Dispersion

Method of SD Preparation[4, 56]	Substance used	Advantages	Mechanism
Fusion Method	Poly ethylene glycol Poly vinyl alcohol	Easy and Economical	Melting the drug within the carrier followed by cooling and pulverization of the obtained product.
Hot Melt Extrusion	Micro crystalline cellulose	Increase in stability and dissolution	With high speed extrusion of the drug and carrier, previously mixed, at melting temperature for a small period of time.
Solvent Method	Tweens and Polyvinylpyrrolidone	Lipophilic drugs are dissolved	Solubilization of the drug and carrier in a volatile solvent that is later evaporated
Supercritical Fluid Method	CO_2 and N_2	Increase in surface area of product	Dissolving the drug and the carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with CO_2.
Electrostatic Spinning Method	HPMC	Nanosized product	Introduction of a liquid into an electric field whereby the liquid is caused to produce fibres. After being drawn from the liquid the fiber harden, which may involve mere cooling, chemical hardening or evaporation of solvent, and then hardened fiber may be collected upon a suitably charged surface
Freeze Drying	Liquid N_2	Less thermal stress	Drying of dispersion in liquid nitrogen
Melt Agglomeration	Ethyl Cellulose and HPMC	Produce stable product	Mixing of drug in hot molten carrier

Research Materialized in Melting Method

- Shivalingam MR *et al* 2011 concluded that 1: 3 ratio of drug and carrier shows better phase solubility and *in vitro* dissolution rate of solid dispersions of glipizide[57].
- Bobe KR *et al* 2011 observed that solid dispersion of atorvatstatin with PEG 4000 had shown enhanced solubility with improved dissolution rate as compared with PVP-K30[58].
- Jafar M *et al* 2010 revealed that solid dispersion of meloxicam showed higher solubility and dissolution as compared to pure drug[59].

Table 5: Carriers Used for Solubility Enhancement

S. No.	Category Examples of carrier[60]
1.	Sugars, Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, lactose.
2.	Acids Citric acid, succinic acid
3.	Polymeric materials Povidone (PVP), polyethylene glycol (PEG), Hydroxypropyl methyl cellulose, methyl cellulose, hydroxy ethyl cellulose, cyclodextrin, hydroxy propyl cellulose, galactomannan.
4.	Hydrotrops Urea, Nicotinamide, Sodium benzoate, Sodium salicylate, Sodium acetate, Sodium-o-hydroxy benzoate
5.	Surfactants Polyoxyethylene stearate, renex, poloxamer 188, texafor AIP, deoxycholic acid, tweens, spans
6.	Insoluble or enteric Hydroxy propyl methyl cellulose phthalate, Polymer Eudragit L100, Eudragit S100, Eudragit RL, Eudragit RS

Table 6: Several Marketed Products Designed by Solid Dispersion

Product[61]	Dispersion Polymer	Technique	Company
Gris-PEG® (Griseofulvin)	Polyethylene glycol	Melt process	Novartis
Sproramax capsules (Itraconazole)	HPMC	Spray layering	Janseen Pharmaceutica
Cesamet®(Nabilone)	Povidone	process unknown	Lilly
Kaletra (lopinavir and ritonavir)	PVP	Melt-extrusion	Abbott Laboratories
Torcetrapiba	HPMC	Spray drying	Pfizer
Ibuprofen	Various Polymers	Melt-extrusion	Soliqs
Isoptin SRE-240 (Verapamil)	Various Polymers	Melt-extrusion	Soliqs
Rezulinb (Troglitazone)	PVP	Melt-extrusion	Pfizer
LCP-Tacro (Tracrolimus)	HPMC	Melt-granulation	Life Cycle Pharma
Certican (Everolimus)	HPMC	Melt or Spray drying	Novartis
Afeditab (Nifedipine)	Poloxomer or PVP	Melt/absorb on carrier	Élan Corp.

Co-Solvency

The addition of a water-miscible or partially miscible organic solvent (i.e. co solvent to water) is a common and effective method to increase solubility of a non polar drug. The technique is known as co solvency or solvent blending. The solubility of a poorly water soluble drug can be increased frequently by the addition of a water miscible solvent in which the drug has good solubility known as co solvents. Co-solvents are mixtures of water and one or more water miscible solvents used to create a solution with enhanced solubility for poorly soluble compounds. The hydrophobic drugs can result in enhancing their solubility by co-solvent as most of co-solvents contain hydrogen bond donor and / or acceptor groups with little part of hydrocarbon regions. Hydrophilic hydrogen bonding groups ensure water miscibility and hydrophobic hydrocarbon regions interfere with water's hydrogen bonding formation, and thus result to reduce the whole intermolecular attraction of water. As a result, co-solvent may enhance the solubility by interfering with water's self-association and decreasing water's ability to pull out non-polar, hydrophobic components[62]. Co-solvent formulations of poorly soluble drugs can be administered orally and parenterally. Parenteral formulations may require the addition of water or a dilution step with an aqueous media to lower the solvent concentration prior to administration. Poorly soluble compounds which are lipophilic or highly crystalline that have a high solubility in the solvent mixture may be suited to a co-solvent approach. Co-solvents may be combined with other solubilization techniques and pH adjustment to further increase solubility of poorly soluble

compounds. The most frequently used low toxic co solvents for parenteral use are propylene glycol, ethanol, glycerine and polyethylene glycol. Dimethylsulfoxide (DMSO) and dimethylacetoamide (DMA). The technique offers several advantages viz. simple and rapid formation and no toxicity problems if compared with surfactants when given parentally. Cell lysis due to high tonicity, toxic effect on renal, central nervous system, hepatic, cardio vascular system are drawbacks associated with this technique[48].

Research Materialized in Co-solvency

- Yeh MK *et al* 2009 revealed that the volume ratio of 5:4:1 in the DMSO / polyethoxylated castor oil / ethanol system resulted in a more suitable vehicle than other systems, with a high solubility (20.73 mg / ml) and low viscosity (10.0 Cp) of tenoxicam[63].
- Seedher M *et al* 2009 observed that upto 763, 316, 153, 524, 297, 792 and 513 times increase in solubility could be achieved in the case of gliclazide, glyburide, glimepiride, glipizide, repaglinide, pioglitazone and rosiglitazone, respectively with co solvency effect[64].
- Tirunagiri M *et al* 2012 found an increase in solubility of flurbiprofen with PEG 400, propylene glycol and ethanol of 7.38 times, 19.43 times and 12.34 times respectively[65].

Liquisolid Technique

Liquisolid compacts possess acceptable flow ability and compressibility properties. They are prepared by simple blending with selected powder excipients referred to as the carriers and the coating materials[66]. The drug in the solid dosage form is held within the powder substrate in a solution or in a solubilized, almost molecular dispersion level, which is the main reason for its significant change in the wetting properties and effective surface area. The drug available for dissolution is increased and hence show enhanced drug release characteristics and improved oral bioavailability. The carrier and coating powder material can retain only certain amounts of liquid while maintaining acceptable flow and compression properties depending on the excipients ratio. The compactions techniques can be proceeded via direct compression method and slugging method[67]. Number of water-insoluble solid drugs can be formulated into liquisolid systems. The method can be applied to formulate liquid medications such as oily liquid drugs. Better availability of an orally administered water insoluble drug, lower production cost than that of soft gelatin capsules, molecularly dispersed of drug in the formulation and capability of industrial production are several benefits of this technique. Low drug loading capacities and requirement of high solubility of drug in non-volatile liquid vehicles are the factors limiting the wide application of the technique[68]. Drugs, non volatile solvent (hydrophilic or lipophilic in nature based on selection of type of formulation like immediate or control release), carrier material (methyl cellulose, ethyl cellulose, starch etc), coating material (nano meter sized silica i.e. aerosil, talc) and disintegrant / superdisintegrants like sodium starch gylcolate and crosspovidone etc are required for the formulation[69].

Research Materialized in Liquisolid Technique

- Elkordy AA *et al* 2012 observed 30 % increases in dissolution of griseofulvin when formulated by liquidsolid technique[70].
- Lakshmi PK *et al* 2011 proved that liquisolid formulation of valsartan show higher dissolution profiles than other formulations[71].
- Gubbi S *et al* 2009 found that liquisolid compact of bromhexine hydrochloride made in propylene glycol show better dissolution rate than bromhexine hydrochloride with PEG 400[72].
- Fenofibrate, griseofulvin and lemotrazine were formulated into granules by slugging and liquisolid compaction technique. The prepared granules were evaluated for solubility, dissolution, wettability and other physicochemical properties. The granules prepared by liquisolid compaction technique shows improvement in solubility, dissolution, wettability and other physicochemical properties comparative to granules by compaction (slugging) technique and raw crystals of drug substances[66].

pH Adjustment

The absorption of a drug is largely dependent upon diffusion, which varies with the pKa of the drug and the pH of the individual regions within the gastrointestinal tract and permeability. The importance of salt selection and pH adjustment has been stressed as a critical parameter of pre formulation, the use of pH-altering excipients within drug delivery systems is also of significant utility. Solubilised excipients that increase environmental pH within a dosage form, such as a tablet or capsule, to a range higher than pKa of weakly acidic drugs increases the solubility of that drug, those excipients which act as alkalizing agents may increase the solubility of weakly basic drugs[73]. If the precipitation upon dilution is fine or amorphous, bioavailability can be increased due to an increased concentration gradient and enhanced surface area for dissolution. In situations where the drug precipitates into poorly soluble particles that require dissolution and do not rapidly dissolve, bioavailability may not be sufficiently increased. pH adjustment is also frequently combined with co solvents to further increase the solubility of the poorly soluble drug[74]. One or more electrolytes are included within the dosage form whose pKa is complementary to the drug; as the dosage form hydrates, the electrolyte is wetted simultaneously with the active compound, creating a micro environment independent of gastrointestinal pH. Micro environmental pH may be modulated to enhance dissolution of poorly soluble drugs via salting-in effects through the inclusion of electrolytes of varying hydrophobic character; conversely, intra-dosage form pH may induce precipitation of highly soluble drugs, thereby slowing dissolution through salting-out effects[73]. There are some serious disadvantages like risk for precipitation upon dilution with aqueous media having a pH at which the compound is less soluble. Intravenously this may lead to emboli, orally it may cause variability and toxicity (local and systemic) related with the use of a non physiological and extreme pH. Another problem with this adjustment is that selected pH may accelerate hydrolysis or catalyze other degradation mechanisms because a dissolved drug in an aqueous environment is frequently less stable chemically compared to crystalline solid[75].

Research Materialized with Change in pH

- Tinwalla AY *et al* 1993 increased the solubility of low water solubility drug thiazolyl benzimidazole at pH =2[76].

- Gladys G *et al* 2003 revealed that solubilization of sulfisoxazole improved by ionization of the drug molecule through pH adjustments[77].

Hydrotropy Method

The term hydrotropy designates the increase in aqueous solubility of various poorly water soluble compounds due to the presence of large amount of additives. Concentrated solutions of sodium benzoate, sodium-o-hydroxy benzoate, sodium-p-hydroxy benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate have been employed to enhance the aqueous solubility of a large number of drugs. Enhancement in solubility of the drugs is due to salting in effect or due to change in solvent character i.e. hydrotrope solubilization phenomenon. The advantages of this phenomenon include simplicity of method, cost effective, environmentally friendly, easily scale up to industrial level[78]. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents and the solute. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Specific examples include ethanol, aromatic alcohols like resorcinol, urea, sodium ascorbate, pyrogallol, catechol, *a*- and *b*-naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids and dodecylated oxidibenzene[48].

Research Materialized with Hydrotropy

- Patel SK *et al* 2011 revealed that sodium benzoate as a hydrotropic agent increases the solubility of ibuprofen at 25°C[79].
- Dhinakaran M *et al* 2012 increased the solubility of amino nitrobenzene by using hydrotropic agents like sodium benzoate, sodium saccharin, dimethyl benzamide[80].

Supercritical Fluid (SCF)

Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp), allowing it to assume the properties of both a liquid and a gas. At near critical temperature, SCFs are highly compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power. Once the drug particles are solubilised within SCF, they may be re crystallized at greatly reduced particle size. Carbon dioxide and water are the most commonly used supercritical fluids. The SCF process can create nanoparticulate suspensions of particles 5–2,000 nm in diameter[47]. Several pharmaceutical companies, such as Nektar Therapeutics and Lavipharm, are specializing particle engineering via SCF technologies for particle size reduction and solubility enhancement. Rapid expansions of supercritical solutions, precipitation with compressed fluid anti solvent, impregnation or infusion of polymers with bioactive materials are the basic techniques in SCF technology[81].

Research Materialized in SCF Method

- Jarmer DJ *et al* 2005 revealed that griseofulvin crystals can be achieved with 100 % dissolution within 60 minutes in a simulated gastric fluid when formulated by supercritical fluid crystallization technique[82].
- Velaga SP *et al* 2002 found that micro particles of crystalline budesonide prepared by SFC and polymorphs of flunisolide produced show enhanced dissolution[83].

Superdisintegrates

Disintegrants are substances or mixture of substances added to the drug formulations, which facilitate dispersion or breakup of tablets and contents of capsules into smaller particles for quick dissolution. These also facilitate the faster disintegration with smaller quantity in contrast to disintegrants. Mechanism for some commercially available super disintegrants is shown in Table 7. Disintegration of dosage forms depends upon various factors of super disintegrants viz. percentage of disintegrants present in the formulation, compatibility with other excipients, presence of surfactants, hardness of the tablets, nature of drug substances, mixing and types of addition etc[84].

Table 7: Superdisintegrants and Their Properties

Superdisintegrants[34]	Commercially available grades	Mechanism of action
Sodium Starch Glycolate	Explotab and Primogel	Rapid absorption of water and increase in volume of granules results fast and uniform disintegration.
Crosslinked cellulose	Crosscarmellose® Ac-Di-Sol®, Nymce ZSX® Primellose®, Solutab®, Vivasol®, L-HPC.	Swells 4-8 folds in < 10 seconds. Swelling and wicking both.
Crosslinked PVP	Crosspovidon M® Kollidon® Polyplasdone®	Swells very little and returns to original size after compression but act by capillary action.
Crosslinked starch	Explotab® Primogel®	Swells 7-12 folds in < 30 Seconds.
Crosslinked alginic acid	Alginic acid NF	Rapid swelling in aqueous medium or wicking action.
Soy polysaccharides	Emcosoy®	Wicking action.

Research Materialized with Superdisintegrants

- Dixit RP *et al* 2007 prepared celecoxib solid dispersion by cogrinding and co evaporation with different carrier. *In vitro* study revealed improved dissolution and disintegration with sodium starch glycolate (SSG)[85].
- Kalyanwat R *et al* 2011 enhanced the dissolution rate of carbamazepine by solid dispersion with two types of superdisintegrants croscarmellose sodium and SSG. The dissolution rate of carbamazepine was reported to be increasing with superdisintegrant addition[86].
- Chaulang G *et al* 2009 prepared solid dispersion of furosemide with SSG in different ratios and by different method. Dissolution data indicated that furosemide dissolution was enhanced[87].
- Rane Y *et al* 2007 studied dissolution enhancement efficiency and solid dispersion formation ability of

hydrophilic swellable polymers such as sodium carboxymethyl cellulose (Na-CMC), sodium starch glycolate (SSG), pregelatinized starch (PGS) and hydroxypropylmethyl cellulose (HPMC) with carbamazepine using 32 full factorial design for each of the polymers[88].

- Patel PA *et al* 2011 worked on aceclofenac, low soluble in water, to increase the water solubility by using ß-cyclodextrin and croscarmellose. The solid dispersions were prepared by using three different methods like physical mixture, kneading method and solvent evaporation technique. The enhanced dissolution was reported[89].
- Gill B *et al* 2010 attempted to increase the solubility of Glimepiride, poorly water soluble drug, by formulating solid dispersion (SD) using Poloxamer 188 (PXM 188) as polymer and then formulating SDs tablets of the best formulation of SDs[90].
- Darwish MK *et al* 2009 prepared solid dispersions consisting of tenoxicam, poorly water soluble drug, with two different types of polymers. The enhancement in the dissolution rate was reported[91].
- Nagabhushanam MV *et al* 2009 formulated the solid dispersions of celecoxib into tablet dosage forms. The increasing order of dissolution rate of formulated tablets with various carriers was croscarmellose > pregelatinised starch > primojel > crospovidone[92].

CONCLUSION

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

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