Sneha Jagtap et al /J. Pharm. Sci. & Res. Vol. 10(9), 2018, 2205-2211

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Solubility Enhancement Technique: A Review

Sneha Jagtap[*1], Chandrakant Magdum[2], Dhanraj Jadge[1], Rajesh Jagtap[1]

1 Annasaheb Dange College of B Pharmacy, Ashta, Sangli – 416301, Maharashtra, India.
2 Rajarambapu College of Pharmacy, Kasegaon, Sangli – 415404, Maharashtra, India.

Abstract

Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous molecular dispersion which is essential to drug's success. But majority of the active pharmaceutical ingredients are poor aqueous soluble, hydrophobic. The solubility, property of the drugs becomes one of the most challenging aspects in formulation development. Poor aqueous solubility results in important products not reaching the finished pharmaceuticals due to not achieving their full potential and therapeutic range. Hence poor aqueous solubility of drugs is major limiting factor with many new drugs in their successful launch in market inspite of their potential pharmacokinetic activity. Molecules that would have highly beneficial effect on their physiological target would not be further developed if their bioavailability is limited by their solubility in water. Aqueous solubility of drug also affects physical, chemical properties of the drug, dose, stability in gastrointestinal track, severs as standard for test of purity, the rate of dissolution of solid, rate and extent of absorption, achieve desired concentration of drug in systemic circulation for desired (anticipated) pharmacological response. Thus solubility is a most important concept presenting itself as valuable contributor in the formulation of pharmaceuticals. If the molecule has to survive the pharmaceutical development process the formulation scientist has to come up with new API with great demand in market. The usable pharmaceuticals with poor solubility must be answered well by solubilization techniques such as chemical modification which involve use of solubilizer such as soluplus, povacoat, dendrimers, and physical modification, complexation, use of surfactant which are becoming more and more important to the pharmaceutical sector by opening up pathway to prepare effective and marketable drugs are discussed in present review article.

Key Words: *Solubility, Solubility enhancement, Bioavailability, Novel methods, Dissolution.*

INTRODUCTION:

Solubility is a property of substance in a particular solvent. In quantitative terms it is concentration of dissolved solute in a saturated solution at a specific temperature. In qualitative terms it means continuous interaction of two or more compound to form one phase, clear homogeneous molecular dispersion. It is measured as maximum amount of solute dissolved in a solvent at equilibrium. The resulting solution is called a saturated solution. A solubility chart gives a list of ions and how, when mixed with other ions, they can become precipitates or remain aqueous. [1, 2] Solubility equilibrium is a dynamic equilibrium that occurs when a chemical compound in the solid state exhibits chemical equilibrium with a solution of that compound. Solubility equilibria are important in pharmaceuticals. Drug with poor aqueous solubility (in other words Class II or even Class IV compounds of BCS) presents dissolution related absorption problems. In pharmaceutical sciences, when quantitative data are available solubility may be expressed as parts, molarity, normality, formality, mole fraction percent solution, volume fraction and molality.

Solubility Expression [3]

Definition	Parts of solvent required for one part of solute
Very soluble	Less than 1
Freely soluble	From 1 -10
Soluble	From 10 -30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000 -10,000
Insoluble	Greater than 10,000

Possible Causes for Poor Oral Absorption [4] any drug is said to be poorly soluble when:

1. Aqueous solubility <100µg/ml.
2. Poor dissolution: Intrinsic dissolution rate <0.1 mg/cm^2/min,
3. High molecular weight: (>500), Self association and aggregation.
4. High crystal energy.

Process of Solubilization [5]

Step 1 The process of solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion

Step 2 Molecule of the solid breaks away from the bulk.

Step 3 The feed of solid molecule is integrated into the hole in Solvent.

Biopharmaceutics classification system (BCS) was introduced by US Food and Drug Administration (FDA) and it classify the drug in to four classes according to permeability and solubility. Solubility impediment are faced in the Class II and Class IV of the system facing dissolution as the rate limiting step for the absorption of drug due to low solubility.

BCS Classification of Drug. [6]

Class	Permeability	Solubility
I	High	High
II	High	Low
III	Low	High
IV	Low	Low

Factors Affecting Solubility [1, 5]

Particle size: Particle size affects solubility. As article size decreases, the surface area to volume ratio increases. As the surface area of particle increases it causes greater interaction with solvent. The effect of particle size on solubility can be described by, [5]

$$\frac{S}{S_0} \quad \text{Log} \quad \frac{2\,\gamma V}{2.303\ R\ T\ r}$$

Where,

S is the solubility of infinitely large particles
S_0 is the solubility of fine particles
V is molar volume
γ is the surface tension of the solid
r is the radius of the fine particle
T absolute temperature in degree Kelvin.
R universal gas constant.

Temperature: Solubility affected by temperature. If the solution process absorbs energy then the solubility will increase with

increasing temperature. If the solution process releases energy then the solubility will decrease with increasing temperature. [8]

Molecular size: The solubility of the substance is decreased when molecules have higher molecular weight and higher molecular size because larger molecules are more difficult to surround with solvent molecules in order to solvate the substance.

Nature of solute and solvent: The nature of solute and solvent depends on concentration of solute in specific quantity of solvent at specific temperature. Example: at room temperature in 100gm of water only 1gm of lead (II) chloride can be dissolved while 200 grams of zinc chloride can be dissolved. [4]

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 no effect on solubility.

Polarity: Polarity of both solute and solvent molecules affects the solubility. Generally polar solute molecules will dissolve in polar solvents and non-polar solute molecules will dissolve in non-polar solvents.

Polymorphs: The ability of a substance to crystallize in more than one crystalline form is polymorphism. Polymorph is an agent having ability to crystallize in more than one crystalline form. It is possible that solid can crystallize in different forms or polymorphs. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubility. [4]

TECHNIQUES TO OVERCOME POOR SOLUBILITY [7-14]

I. Chemical Modifications:

1) Salt Formation
2) Co-crystallization
3) Co-solvency
4) Hydrotropy
5) Use of novel solubilizer
6) Nanotechnology

II. Physical Modifications:

1. Particle size reduction

a) Conventional method
b) Micronization
c) Nanosuspension

2. Modification of the crystal habit

a) Polymorphs
b) Pseudopolymorphs

3. Complexation

a) Physical mixture
b) Kneading method
c) Co-precipitate method

4. Inclusion Complex Formulation Based Techniques

a) Kneading method
b) Lyophilization/ Freeze- drying Technique
c) Microwave irradiation method

5. Solubilization by surfactants

a) Microemulsions
b) Self microemulsifying drug delivery system

6. Drug dispersion in carriers

a) Solid solutions
b) Solid dispersions
   i. Fusion Process
   ii. Solvent Method
   iii. Fusion solvent method
   iv. Spray drying
   v. Lyophilization (Spray Freeze Drying Method)
   vi. Hot melt Extrusion
   vii. Dropping Method

III. pH adjustment
IV. Supercritical fluid process
V. Liquisolid technique
VI. Polymeric alteration

I. CHEMICAL MODIFICATIONS

1. Salt formation:

Many a times an API cannot be formulated in its pure form due to various issues of instability. Thus they are converted to solid forms such as salts, co-crystals, solvates, hydrates, and polymorphs. Each of them imparts a different physiochemical property and affects performance characteristics stability, bioavailability, purification and manufacturability of the drug in their own better way. Salt formation of poorly soluble drug candidates (weak acids and bases) has been a strategy for several decades to enhance solubility. Salts are formed when a compound is ionized in solution. It is an effective method in parenteral and other liquid formulations, as well as in solid dosage forms. Acidic or basic drug converted into salt having more solubility than respective drug. Ex. Aspirin, Theophylline, Barbiturates. Commercially available example of this approach is Progesterone; a water-insoluble steroid which is solubilized in peanut oil [15].

2. Co-crystallization: [16] Co-crystallization alters the molecular interactions and is considered promising alternative to optimize drug properties. A more refined definition of a co-crystal can be "multicomponent crystal that is formed between two compounds that are solids under ambient conditions, where at least one component is an acceptable ion or molecule. Co-crystallization overcomes various physical, chemical or physiological drawbacks of an API. Mechanism of co solvency favors the dissolution of a non-polar solute by lowering the interfacial tension. The most appropriate co-crystal can be selected using analytical techniques and rational physicochemical studies that include investigations of solubility and stability. The only difference between solvates and cocrystals is the physical state of the components. If one of the components is liquid and the other is solid then it is termed as solvates but on the other hand if both exists in solid form then they are termed as cocrystals. Pharmaceutical Co-crystals basically consists of two components that are the API and the co-crystal former(s).

Different techniques for co crystallization 1)Solvent evaporation 2)Grinding 3)Slurry Co - Crystallization 4)Solvent drop grinding (Modification of Grinding) 5)High throughput co-crystallization (17) 6)Hot melt extrusion 7) Sonocrystallization Method.

Co Crystals Characterization Parameters 1) Solubility 2) Maximum wavelength 3) Stability 4) Intrinsic dissolution 5) Bioavailability 6) Melting Point 7) Melt (Hot stage microscopy) 8) Scanning Calorimetry (DSC) 9) XRD 10) Vibrational spectroscopy.

3. Co-solvency/Solvent Blending: It enhances solubility of poor water soluble drug by the addition of water miscible solvent in which drug has good solubility by reducing the interfacial tension between the aqueous solution and hydrophobic solute. The pharmaceutical form is always liquid. Poorly soluble compounds which are lipophillic or highly crystalline that have a high solubility in the solvent mixture may be suited to a co-solvent approach. It has found its main use in parenteral dosage forms because of low toxicity of many co-solvents, and relatively greater ability of co-solvents to solubilise nonpolar drugs. **Commonmly used cosolvents** Glycerol, propylene glycol, PEG 400, Dimethyl Sulfoxide, Dimethyl Acetamide, Ethanol, n-Octanol are the commonly used cosolvents. [18, 19]

Advantages of co-solvency/solvent Blending

1. Has large solubilization capacity for poorly soluble drugs, simple and rapid to formulate, produce and evaluate.
2. It can be combined with other solubilization techniques and pH adjustment to further increase solubility of poorly soluble compounds.

Disadvantages of co-solvency/solvent Blending

1. Toxicity and tolerability related with the level of solvent administered has to be considered
2. Sometimes even uncontrolled precipitation occurs upon dilution with aqueous media. The precipitates may be amorphous or crystalline and can vary in size.
3. Many of the insoluble compounds are unsuited to co-solvents, particularly for intravenous administration. The drugs which are extremely insoluble in water and do not readily redissolve after precipitation from the co- solvent mixture may have a potential risk for embolism and local adverse effects at the injection site.
4. As with all solubilized forms, the chemical stability of the insoluble drug is worse than in a crystalline state.

4. Hydrotrophy: Is a solubilization phenomenon where addition of a large amount of second solute results in an increase in the aqueous solubility of existing solute. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotropic agents like sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs. Hydrotropic agents are ionic organic salts. Hydrotropic solutions do not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute. [20] Classification of hydrotropes. [19]

Category	Example
Aromatic anionics	Sodium benzoate, Sodium salicylate, Sodium benzene sulphonate, Sodium benzene disulphonate, Sodium cinnamate.
Aromatic cationics	Para amino benzoic acid hydrochloride, Procaine hydrochloride, Caffeine.
Aliphatics and linear anionics	Sodium alkanoate.

Advantages of hydrotrophy

1. Hydrotropy is suggested to be superior to other solubilization method, such as miscibility, micellar solubilization, co solvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification.
2. Solvent character is independent of pH, hydrotrophy has high selectivity and does not require emulsification.
3. It only requires mixing the drug with the hydrotrope in water and do not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.
4. Wide variety of compounds has been reported to exhibit hydrotropic behavior. Examples may include ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, and b-naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate) and dodecylated oxidibenzene.

Mixed Hydrotropy [21]: It is new, simple, cost effective, safe, accurate, precise method which involves the blends of hydrotropes which gives synergistic effect on solubility of poorly water soluble drug.

Advantages of mixed hydrotropy

1. It may reduce the large total concentration of hydrotropic agents necessary to produce modest increase in solubility by employing combination of agents in lower concentration.
2. The use of hydrotropic solubilizers as permeation enhancers.
3. Application of hydrotropic solubilisation in nanotechnology (by controlled precipitation).

5. Use of novel solubilizer: The solubility of poorly soluble drug can also be improved by various solubilizing materials. Ex. Conventional solubilizer Polysorbates, PEG 400 Sepitrap, [22] Soluplus [23] Povacoat, dendrimers, is improve the solubility of hydrophobic API.

Sepitrap as novel Solubilizer In less than 5 minutes, 80 % of solubilizers are desorbed from Sepitrap^{TM} (Microencapsulated solubilizer for solid dosage application) and therefore is available to solubilize the drug substance. The ratio of sepitrap and drug (2:1) is good for enhancing dissolution rate and at the same time does not affect tablets characteristics and can be used without any formulation constraints. [24]

Dendrimers [25] act as solubilizing agents to host both hydrophilic and hydrophobic drugs and are known for their three dimensional, monodispersed, highly branched, macromolecular nano-scopic architecture with number of reactive end groups obtained by reiterative sequence of reactions. Dendrimers are considered as static unimolecular micelles and their micellar structure remains stable at even higher concentrations of solvents. Micelle-like behaviour of dendrimers resulted into their application to solubilize hydrophobic drugs. Dendrimers enhance the solubility of hydrophobes probably due to hydrophobic interactions, hydrogen bonding and electrostatic interaction between terminal functional groups of the dendrimers and hydrophobes. Most common dendrimers are polyamidoamine (PAMAM) dendrimers polypropyleneimine (PPI) dendrimers. Literature suggests that PAMAM dendrimers are the most investigated dendrimers in solubilization. Poly (propylene)imine dendrimers (PPI) constitute an equally important family of dendrimers reported first by Brabander and Meijer. These dendrimers closely resemble PAMAM dendrimers (except repeating units).

6. Nanotechnology: Refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometres (nm) or less. For many new chemical entities of very low solubility, oral bioavailability enhancement by micronization is not sufficient because micronized product has very low effective surface area for dissolution and next step taken was nanonisation [26]. The methods of preparation like milling, high pressure homogenization, vacuum deposition, and high temperature evaporation may be used.

Advantages of nanotechnology

It results in production of the nano or micro sized spherical particles with smooth surfaces and narrow particle size distribution and high specific surface areas, consequently increasing the dissolution rate and solubility.

Disadvantage of nanotechnology

The agglomeration problem is inherent and difficult to overcome.

II. PHYSICAL MODIFICATIONS:

1. Particle size reduction Solubility of drug is often intrinsically related to drug particle size. As particle size become smaller, surface area to volume ratio increases. Larger surface area allows grater interaction with the solvent which causes an increase in solubility. The bioavailability of poorly soluble drugs is often related to drug particle size. Increased surface area by reducing particle size improves the dissolution properties and allows a wider range of formulation approaches and delivery technologies. [27, 28]

Advantages of particle size reduction

1. It is efficient, reproducible, economic means of solubility enhancement.

2. Increase the rate of solution in case of chemical substances, because reduction of particle size increases the surface area for the action of solvent.
3. Allows rapid penetration of solvent.

Disadvantages of particle size reduction

1. Due to high surface charge on discrete small particles, there is strong tendency for particle agglomeration.
2. Physical, mechanical stress may induce degradation of active compound.
3. Thermal stress which occurs during comminution may present problems in processing of thermosensitive agents.
4. Developing solid dosage form with a high pay load without encouraging agglomeration and sterile intravenous formulation is technically challenging.

a) Conventional method of particle size reduction Different mechanisms involved in conventional method of particle size reduction are cutting, compression, impact, attrition, combined impact and attrition. 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 economic, reproducible, and efficient means of solubility improvement. However, the mechanical forces natural 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 considered when processing thermo sensitive or unstable active agents. Only by using traditional methods of solubility enhancement it is not possible to increase the solubility of poorly soluble drugs upto desirable level.

b) Micronization: It is a high energy particle size reduction technique that can convert coarse particles into particles of less than 5 μ in diameter. Micronization results in uniform and narrow particle size distribution essential for developing uniform dosage form. As micronization occurs surface area increases with decreasing particle size and solubility increases. The properties of the micronized drug substance such as particle size, size distribution, shape, surface properties, and agglomeration behavior and powder flow are affected by the type of micronization technique used. Mechanical communition, spray drying and supercritical fluid (SCF) technology are the most commonly employed techniques for production of micronized drug particles. According to the Noyes–Whitney postulations, the administration of a drug in micron size is a prominent method to improve bioavailability of poorly water soluble drug substances.

Techniques for Micronization

a) Jet milling /fluid energy mill or micronizer
b) Rotor stator colloids mills
c) Microprecipitation & microcrystallization
d) Controlled crystallization
e) Supercritical fluid technology
f) Spray freezing in to liquid

Advantages of micronization

1. Gives uniform particle with increase in surface area and narrow particle size distribution.

Disadvantages of micronization

1. High energy process, which causes disruption in the drug crystal lattice and this, may result in presence of disordered or amorphous regions in the final product.
2. Amorphous regions are thermodynamically unstable and are susceptible to recrystallization upon storage particularly in hot and humid conditions.

c) Nanosuspension: This technology is applied to poorly soluble drugs that are insoluble in both water and oils. A pharmaceutical nanosuspension is biphasic systems consisting of nano sized drug particles in aqueous vehicle stabilized by surfactants for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm. [29] Nanosuspension is produced by bottom up technology and top down technology. Top down technology involves various methods such as nano edege, nanojet technology, milling tech (Nanocrystals).

Advantages of nanosuspension

1. In nanosuspension the particle size of drug is reduced which increases the surface area which in turn increases solubility, dissolution rate, and ultimately bioavailability.
2. Nanosuspension results in permeability enhancement.
3. Nanosuspension results in increases in bioadhesion and duration of action of residence.
4. Nanoformulation exerts advantage of high drug loading.
5. Avoidance of organic solvent.

Disadvantages of nanosuspension

Suffers from problem of instability due to agglomeration, crystal growth, Ostwald ripening.

2. Modification of the crystal habit

a) Polymorphs
b) Pseudopolymorphs

Polymorphism is the ability of an element or compound to crystallize in more than one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability. Similarly amorphous form of drug is always more suited than crystalline form due to higher energy associated and increase in surface area. Order for dissolution of different solid forms of drug Amorphous >Metastable polymorph >Stable polymorph

3. Complexation: Is the association between two or more molecules to form a non bonded entity with a well defined stoichiometry. [30] Two type of complex:

Stacking complexes: It is driven by association of non polar area of drug and complexes agent this results in exclusion of the non polar area from contact with water. Stacking can be homogeneous or mixed, but results in clear solution.

Inclusion complexes: It is formed by the inserting the nonpolar molecule, region of one molecule into the cavity of another molecule or group of molecules. Cyclodextrine and their derivatives commonly used in complexation.

Solid ternary complexes can be formed with

1. Carboxylic acid [31] – eg. citric acid, tartaric acid
2. Water soluble polymer[32] – Soluplus,[23] Povacoat, Kollidon,
3. Amino acid [33]- Arginine, tryptophan, leucine, phenylalanine, methionine, and isoleucine
4. Sugar alcohol[34] – Mannitol

Ternary agent helps in binding of drug and with complexing agent.

Most probably use of acidic ternary compound in case of basic drug or vice versa that is use of basic ternary compound with acidic drug is done to form solid ternary complex.

Water soluble polymer may be used in specific concentration for example 0.5% or 1% by preparing its aqueous solution.

Drug, B-CD and amino acid such as L- Lysine and Arginine ternary complexes may be prepared at 1:1:2 molar ratios, or weight ratio or other suitable ratio.

a) Physical mixture In this the CDs or suitable polymer and drug are mixed together thoroughly by trituration in a mortar and passes through appropriate sieve to get the desired particle size in the final product. It is simple trituration method.

b) Kneading method This method is based on soaking the CDs or suitable polymer with little amount of water or hydro alcoholic solutions to converted into a paste. The drug is then added to the above paste and kneaded for a specified time. The kneaded mixture is then dried and passed through sieve.

c) Co-precipitate method: The required amount of drug is added in the solution of CDs or suitable polymer. The complex kept under magnetic agitation with controlled process parameters. The complex is 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. This method is applicable to industry.

4.Inclusion Complex Formulation Based Techniques

Inclusion complexes are formed by the lodging of the nonpolar molecule or nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). Commonly used host molecules are cyclodextrins. The cavity of host must be large enough to accommodate the guest and small enough to eliminate water, Solid inclusion complexes are prepared by various methods such as kneading method co-precipitation, neutralization, co-grinding, spray drying method, and microwave irradiation method. [35]

a) Kneading method: discussed in complexation

b) Lyophilization/Freeze-Drying Technique: In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug and CDs or suitable polymer at reduced pressure. Lyophilization in great measure dependent on unique properties of water and its role as solvent, gas, diluents, plasticizer, stabilizer. It is an alternative to solvent evaporation and involves molecular mixing of drug and carrier in a common solvent.

Advantages of lyophilization/freeze-drying technique

1. Lyophilization/freeze drying technique is considered worthy to get a porous, amorphous powder with high degree of interaction between drug and suitable polymer.
2. Thermolabile substances can be successfully made into complex form by this method.

Disadvantages of lyophilization/freeze-drying technique

1. Use of specialized equipment.
2. Time consuming process, and yield poor flowing powdered product.

c) Microwave Irradiation Method: 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 bottom flask. The mixture is reacted for short time of about one to two minutes at 60 ºc 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 is separated by whatman filter paper, and dried in vacuum oven at 40 ºc for 48 hrs.

5. Solubilization by surfactants: Surfactants are molecules with polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. 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 of most importance in industrial and natural processes. The addition of surfactants decreases the surface tension and increase the solubility of the drug by increasing the dissolution of lipophilic drugs in aqueous medium. 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 and is known as micellization and predominantly results in elevated solubility of poorly soluble drugs.

a) Microemulsions: A micro emulsion is an optically clear pre-concentrate, isotropic, thermo dynamically stable transparent, translucent system, containing a mixture of oil, hydrophilic surfactant and hydrophilic solvent which dissolves a poorly water soluble drug. The criteria for the selection of surfactant are HLB and non-toxicity. On contact with water, the formulations self emulsifies and forms a very clear emulsion of small and uniform oil droplets containing the solubilized poorly soluble drug. Micro-emulsions have been employed to increase the solubility of many drugs that are practically insoluble in water, along with incorporation of proteins for oral, parenteral. Oil-in-water (o/w) microemulsion is the most suitable formulation, which is expected to increase the solubility by dissolving compounds with low water solubility into an oil phase. They can also enhance oral bioavailability by reducing the droplet size (< 100 nm), and hence increase the rate of absorption due to surfactant-induced permeability changes. [14]

Advantages of microemulsions

Simplicity of preparation, clarity, ability to be filtered and incorporate a wide range of drugs of varying solubility.

b) Self-emulsifying drug delivery systems: Uses 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). Self-emulsifying drug delivery systems (SEDDS) and self microemulsifying drug delivery systems (SMEDDS) are isotropic solutions of oil and surfactant which form oil-in-water microemulsions on mild agitation in the presence of water. These novel colloidal formulations on oral administration behave like oil-in-water microemulsions.

6. Drug dispersion in carriers [36]: Solid solution is blend of two crystalline solids that exist as a new crystalline solid. A mixed crystal is formed because the two components crystallize together in a homogenous one-phase system. Hence, it is expected to yield much higher rates of dissolution than simple eutectic systems.

Amorphous precipitation: Amorphous precipitation occurs when drug precipitates as an amorphous form in inert carrier. The higher energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystalline forms of the drug.

Applications of solid dispersions It is possible that such a technique be used: [37]

1. To obtain a homogeneous distribution of a minute amount of drug in solid state.
2. To stabilize the unstable drug.
3. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
4. To formulate a fast release primary dose in a sustained released dosage form.
5. To reduce pre systemic inactivation of drugs like morphine and progesterone.
6. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
7. To convert polymorphs in a given system into isomorphous, solid.

Advantages of solid dispersion [38]

1. It has rapid dissolution rates.
2. Increase absorption rate of drugs.
3. Improve dissolvability in water of a poorly water-soluble drug in a pharmaceutical.
4. Decrease the crystalline structure of drug into amorphous form.

5. Prepare rapid disintegration oral tablets.
6. Mask the taste of the drug substance.
7. Avoid degradation or decomposition of drugs. Transformation of the liquid form of the drug into a solid form (Ex. Clofibrate and Benzoyl benzoate can be incorporated into PEG-6000 to give a solid.)
8. Avoidance of polymorphic changes and there by bioavailability problems,

Disadvantages of solid dispersion [38]

1. Instability of solid dispersion.
2. Moisture and temperature have deteriorating effect on solid dispersion.
3. It shows crystallinity and decrease in dissolution rate with aging.

Limitations of solid dispersion system

1. Poor predictability of solid dispersion behavior due to a lack of a basic understanding of their material properties.
2. There is the possibility that during processing (mechanical stress) or storage (temperature and humidity stress) the amorphous state may undergo crystallization. The effect of moisture on the storage stability of amorphous pharmaceuticals is also of a vital concern, because it may increase drug mobility and promote drug crystallization.
3. Most of the polymers used in solid dispersions have tendency to absorb moisture, which may result in the crystal growth, phase separation, or conversion from the amorphous to the crystalline state during storage which may result in decreased solubility and dissolution rate.
4.

Methods of preparing solid dispersions

i) Fusion Process [39]: The carrier is heated to a temperature just above its melting point and the drug is incorporated into the matrix. The mixture is cooled with constant stirring to homogeneously disperse the drug throughout the matrix. Other factors that may play a role include solubilizing effect conferred by the carrier itself, improved wetting or decreased surface hydrophobicity, complexation, and crystallization of the drug in a metastable polymorphic form of altered thermodynamic properties.

Disadvantages

Exposure of drugs to elevated temperatures, particularly if the carrier is a high-melting solid and the drug is thermoliable.

ii) Solvent Method: The carrier and the active ingredient are dissolved in a suitable organic solvent. This solvent is evaporated at an elevated temperature or under vacuum. As the solvent is being removed, super saturation occurs followed by simultaneous precipitation of the constituents resulting in a solid residue. The co precipitate is then dried under vacuum to drain out any solvent freely adhering to the particle. Removal of even trace amounts of the solvent is implied. Highly sensitive techniques such as differential thermal analysis (DTA), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and less sensitive procedures like spectroscopy, gravimetry and can be used to demonstrate complete solvent removal. [40]

iii) Fusion-Solvent Method: Carrier(s) is/are melted and the drug(s) is/are incorporated in the form of a solution. If the carrier is capable of holding a certain proportion of liquid yet maintaining its solid properties, and if the liquid is innocuous, the need for solvent removal is eliminated. Method is useful for drugs with high melting points or that are thermolabile.

iv) Spray Drying: The carrier and the active ingredient are dissolved, suspend in a suitable solvent. This solvent is evaporated by drying it to apply a stream of heated air to remove the solvent. Due to the large surface area of the droplets, the solvent rapidly evaporates and solid dispersion is formed quickly.

v) Lyophilization (Spray Freeze Drying Method) this method has been successfully developed to prepare solid dispersions at ambient temperature and avoid the heating during the preparation of thermosensitive drugs; spray freeze drying (SFD). SFD technology involves the atomization of a feed liquid containing poorly water-soluble or insoluble APIs and excipients directly into a cryogenic liquid at ambient temperature to produce a frozen micronized powder that is subsequently dried. This process offers a variety of advantages compared to traditional technologies for solid dispersions, including amorphous structure and high surface area. [41-43]

vi) Hot-melt Extrusion: This is method of choice in the polymer industry. But Speiser and Huttenrach were the first persons who use this technology for pharmaceutical purpose. A melt extrusion consists of the following sections: An opening to feed raw materials, a heated barrel that consists of extruder screws to convey and mix the fed materials, and an exit port, which consists of an optional die to shape the extruding mass. The Active ingredients and the carrier are fed into the heated barrel of extruder at a constant rate. When the mixture of active ingredient and the carrier is conveyed through heated screws, it is transformed into its “fluid like state”. This state allows intimate and homogeneous mixing by the high shear of extruder screws. An exit port, which consists of an optional die, shapes the melt in the required form such as granules, pellets, films, or powder. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about one minute, which enables drug that are somewhat thermolabile to be processed. [44]

vii) Dropping Method: A solid dispersion of a melted drug-carrier mixture is pipetted then dropped onto a plate, where it solidifies into round particles. The size, shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. As viscosity is highly temperature dependent, it is very important to adjust the temperature so that when the melt is dropped on the plate it solidifies to a spherical shape. [45]

III. PH ADJUSTMENT

Poor water soluble drug may potentially dissolve in water by implementing a pH change. To access the solubility by 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. [19]

Advantages of pH adjustment

1. Simple to formulate and analyze.
2. Uses small quantities of compound, amenable to high throughput evaluations.

Disadvantages of pH adjustment

1. 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.
2. Tolerability and toxicity both local and systemic related with the use of a non physiological pH and extreme pH should be considered.
3. As with all solubilized and dissolved systems, a dissolved drug in an aqueous environment is frequently less stable chemically compared to formulations crystalline solid. The selected pH may accelerate hydrolysis or catalyze other degradation mechanisms.

IV. SUPERCRITICAL FLUID PROCESS:

Supercritical fluids (SCFs) can dissolve nonvolatile solvents, with the critical point of carbon dioxide. It is safe, environmentally friendly, and economical. A SCF exists as a single phase above its critical temperature and pressure. SCFs have properties useful to

product processing because they are intermediate between those of pure liquid and gas. 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. Unique processing capabilities of SCFs, long recognized and applied in the food industry have recently been adapted to pharmaceutical applications. Commonly used supercritical solvents are carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water. 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 Impregnation or infusion of polymers with bioactive materials, Compressed Fluid Antisolvent, Solution enhanced Dispersion by Supercritical Fluid, solution enhanced dispersion by SCF (SEDS), aerosol supercritical extraction system (ASES) and supercritical antisolvents processes (SAS) [14]

Advantages of supercritical fluid process

1. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research.
2. Once the drug particles are solubilized within SCF, they may be recrystallized at greatly reduced particle sizes. Current SCF processes have demonstrated the ability to create nano suspensions of particles 5-2,000nm in diameter.
3. The flexibility and precision offered by SCF processes allows micronization of drug particles within narrow ranges of particle size, often to sub-micron levels.

V. LIQUISOLID METHODS

When the drug dissolved in the liquid vehicle is introduced into a carrier material which has a porous surface and fibers in its interior as cellulose, both absorption and adsorption take place; i.e. the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive properties and large specific surface area gives the liquisolid system with desirable flow characteristics. Microcrystalline and amorphous cellulose and silica powders may be used as coating materials. [46]

Advantages of Liquisolid Methods

1. Provides acceptably flowing and compressible powdered forms of liquid medications.
2. Method improves the solubility, bioavailability of orally administered water insoluble and is applicable in industry.
3. Useful for the formulation of oily drugs/liquid drugs.
4. Drug release can be modified by using different carrier and additives like PVP, PEG 60000, Hydroxy Propyl Methyl Cellulose and Eudragit etc.
5. A number of poorly soluble drugs can be formulated in to the system.
6. This system is specifically for the powdered liquid medications.
7. Production cost is low compared to that of preparation of soft gelatin capsules.

Disadvantages of liquisolid method:

1. It requires recipients of high adsorption properties and high specific surface area.
2. It is not applicable to high dose insoluble drugs (>100 mg).

VI. POLYMERIC ALTERATION

Different crystalline forms of a drug that may have different properties are known as Polymorphs. Polymorphs may vary in physicochemical properties such as physical and chemical stability, melting point, vapor pressure, shelf-life, dissolution rate, morphology, density, biological activities intrinsic solubility, bioavailability. Amongst the stable, unstable and metastable crystalline polymorphs, metastable forms are related with higher energy with increased surface area, solubility, bioavailability and efficacy. With regard to bioavailability, it is favored to change drug from crystal forms into metastable or amorphous forms over its shelf-life under a variety of real-world storage conditions.

REFERENCES

1. Aulton, M.E., *Pharmaceutics: The Science of Dosage Form and Design*, Churchill Livingstone, New Delhi 2013.
2. More Hajare, *Physical Pharmacy Practices*, Career publications, Nashik 2013.
3. Indian pharmacopoeia, Government of India ministry of health and family welfare, published by the government of publication, Delhi 2014.
4. Vilas, P. B., Vinayta, R. A., Anirudha, V. M., Arunadevi, S. B., Sanjay, Bais., *J. Innov. Pharm. Biol. Sci*.2015, *2 (4)*, 482-494.
5. Sinko, P.J, *Martin's Physical pharmacy and pharmaceutical science*, Wolters kluwer, New Delhi 2011.
6. Wu, C.Y., Benet, L.S., *Pharmaceutical research*. 2005, *22(1)*, 23-27.
7. Kadam, S.V., Shinkar, D.M., Saudagar, R.B., *Int. j. pharm. biol. sci*. 2013, 3 (3), 462-475.
8. Blagden, N., Matas, M., Gavan, P.T., York, P., *Adv. Drug Delivery Rev*. 2007, *59(7)*, 617–630.
9. Meera, C., *J Pharmacy Res*. 2010, *3(10)*, 2494-2501.
10. Thorat, Y. S, Gonjari I. D, Hosmani A. H., *Int J Pharm Sci Res*.2011, *2(10)*, 2501-2513.
11. Shinde A., *Pharminfo.net*. 2007, *5(6)*, 1-9.
12. Brahmnkar, D.M., Jaiswal, S.B., *Biopharmaceutics and Pharmacokinetics Treatise*. Vallaabh prakashan, Delhi 2009.
13. Leuner, C., Dressman, J., *Euro J Pharm Biopharm*. 2000, *50*, 47-60.
14. Kumar, S., Singh, P., *The Pharm Innov J*. 2016, *5(1)*, 23-28.
15. Serajuddin, A.T, *Adv Drug Deliv Rev*. 2007, *59(7)*, 603-16.
16. Patole, T., Deshpande, A., *Int J Pharm Sci Res*.2014, *5(9)*, 3566-3576.
17. Michihiro, S. A., *PLoS One*. 2014, *9(4)*, 1-8.
18. Chaudhary, A., Nagaich, U., Gulati, N., Sharma, V. K., Khosa, R. L., *J Adv Phar Edu Res*. 2012, *2 (1)*.
19. Vemula, V. R., Lagishetty, V., Lingala, S., *Int. J Pharm Sci Rev Res*. 2010, *5 (1), 41-51*.
20. Nidhi, K., Indrajeet, S., Mehta, K., Karwani, G., Dhrubo, J., Int J *Drug Dev Res*. 2011, *3(2)*, 26-33.
21. Jain, P., Goel, A., Sharma, S., Parmar, M., *International Journal of Pharma Professional's Research*. 2010, *1(1)*, 34-45.
22. Ahmad, D., Setouh., Emad, A.l., , Abdelmelek N.S., *Eur J Pharm Biopharm*.2015, *94*, 386-392.
23. Naveen, K., Thakral, A., R. Ray., Bar-Shalom, D., Eriksson, A. H., Majumdar, D. K., *AAPS Pharm SciTech*. 2012, *13*, 1.
24. Available at www.seppic.com
25. Gupta. U., Bharat. H., Jain. N. K., *J Pharm Sci*. 2007, *10(3)*, 358-67.
26. Sharma, M., Sharma, R., Jain, D. K., *Scientifica* 2016.
27. Chauhan, N.N., Patel, N.V., Suthar S.J., Patel J.K., Patel, M.P., *Res J Pharm Tech*. 2012, *5 (8)* 999-1005.
28. Jadhav, P.A., Metkari, V.B, et al, *J Curr Pharm Res*. 2014, *4(2)*, 1128.
29. Muller, R.H., Peters. K., Becker R., Kruss, B., *Control Release Bioact*. 1995, *22*, 574-575.
30. Patil, J.S., Kadam, D.V., Marapur, S.C., Kamalapur, M.V., *Int J Pharm Sci Res*.2010, *2(2)*, 29-34.
31. Enrico, redenti., lajos, szente., jo,´ zsef, szejtli., *J Pharm Sci*. 2000, *89*, 1–8.
32. Shan-Yang, Lin., Hong-Liang, Lin., Ying-Ting, Chi., Ru-Ying, Hung., Yu-Ting, Huang., Chi-Yu, Kao., Wei-Hsien, Hsieh., *Asian J Pharm Sci*. 2016, *11*, 376–384.
33. Hong, Yang., Cornelia, Bohne., *J. Phys. Chem*. 1996, *100*, 14533-14539.
34. Ghorpade, V. S., Dias, R., Mali, K., Havaldar, V., *Asian J Pharm*. 2016, *10 (3)*, 375.
35. Patil, M. S., Godse1, S. Z., Saudagar, R. B., *World J Pharm Pharm Sci*. 2013, *2(6)*, 4558 -4572.
36. Vippagunta, S.R., Zaren, W., Hornung, S., Krill, S.L., *J Pharm Sci*. 2006, *96*, 230- 294.
37. Kalyanwat, R., Patel, S., *Inter J Drug Formu Res*. 2010,*1 (3)*,1-14.
38. Verma, S., Rawat, A., Kaul, M., Saini, S., *Inter J Pharmacy Tech*. 2011, *3(2)*,1062-1099.
39. Sareen, S., Mathew, G., Joseph, L., *Int J Pharma Investig*. 2012, *2(1)*, 12-17.
40. Yella, S.R., Krishnalah., *Inventi Spreading knowledge*.10-18.
41. Kushwaha, A., *Inter J Pharm Sci Res*. 2011, *2(8)*, 2021-2030.
42. Kalyanwat, R., Patel, S., *Inter J Drug Formu Res*. 2010, *1 (3)*, 1-14.
43. Verma, S., Rawat, A., Kaul, M., Saini, S., *Inter J Pharmacy Tech*. 2011, *3(2)*, 1062-1099.
44. Habib, M.J., Technomic Publishing Company, Inc. Lancaster, Pennsylvania (U.S.A.). 2001, 1-36.
45. Pawar, A.R., Choudhari, P.D., *Asian J. Biomed. Pharm. Sci*. 2012, *13*, 9-14.
46. Pardhi, D., Shivhare, U., Suruse, P., Chabra, G., *Res J Pharm Dosage Forms Tech*. 2010, *2(5)*, 314-322.