WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 16, 1770-1789. Review Article ISSN 2277– 7105

COMPREHENSIVE REVIEW ON SOLUBILITY ENHANCEMENT TECHNIQUES OF HYDROPHOBIC DRUG

Rutika S. Kurkute*, Gayatri G. Mahale, Arya D. Naikare, Suryawanshi Akshada D. and Shelke Mangal M.

Student At/Post Bota Sangmaner Maharashtra India 422602.

Article Received on
19 October 2022,

Revised on 09 Nov. 2022,
Accepted on 29 Nov. 2022

DOI: 10.20959/wjpr202216-26272

***Corresponding Author**
Rutika S. Kurkute
Student At/Post Bota
Sangmaner Maharashtra
India 422602.

ABSTRACT

Solubility, the phenomenon of dissolution of solute in solvent to give a homogenous system, is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired (anticipated) pharmacological response. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. The use of modern drug discovery programs has increased the number of new active pharmaceutical ingredients (API) with high lipophilicity and poor oral absorption. This present review details about Various Solubility enhancement techniques have been used as one of the most effective strategies to enhance the oral bioavailability of these API. The usable pharmaceuticals with poor solubility must be answered well by Solubilization techniques such as chemical modification which involve use of Solubilized such as surplus, 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. Selection of solubility improving method depends on drug property, site of absorption, and required dosage form characteristics.

KEYWORDS: Solubility, Bioavailability, Solubility enhancement, Solid dispersion.

INTRODUCTION

Oral route is most desirable route of administering the dosage form. The major problem faced during the oral administration of active agent is the bioavailability. 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. Recently more than 40% NCEs (new

chemical entities) developed in Pharmaceutical Industry are practically insoluble in water. These poorly water soluble drugs are allied with slow drug absorption leading to inadequate and variable bioavailability and gastrointestinal mucosal toxicity.[1] To solve the solubility problem we discuss the various traditional as well as newer method of solubility enhancement. The traditional method includes solid dispersion, complexation and pH adjustment while newer methods include Liquisolid, hydrotrophy, Sonocrystallisation, self emulsifying system.

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.

Table no. 1: Solubility expression.

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

Process of solubilization

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.

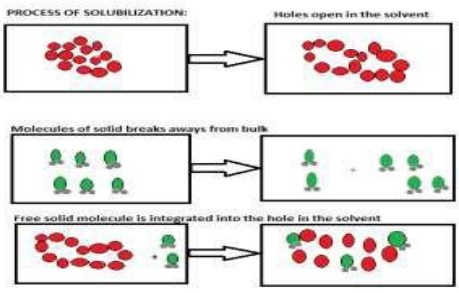

Fig. 01: process of solubilization.

BCS (Biopharmaceutics classification system)

BCS (Biopharmaceutics classification system) classify the drug in to four classes according to their solubility and permeability. Solubility challenges are faced in the Class II and Class IV of the BCS system (where dissolution becomes the rate limiting step for the absorption of drug). which comprises of newer generation of NSAIDs like Zaltoprofen, Aceclofenac, Flurbiprofen, their older congeners like Indomethacin, Ibuprofen, Ketoprofen and Diclofenac; anti-diabetics Gliclazide, Glipizide ; newer calcium channel blockers (CCBs) like Nimodipine, Felodipine.. The BCS was first devised in 1995 by Amidon et al.

BCS Classification of drug.

Table no. 2: [BCS Classification of drug].

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

1. Techniques for solubility enhancement

There are various techniques available to improve the solubility of hydrophobic drugs. Some traditional and novel approaches to improve the solubility are:

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) Co-precipitation

c) Physical blending method

d) Neutralization method

e) Milling/Co-grinding technique

f) Lyophilisation/ Freeze drying technique

g) h. Supercritical antisolvent technique

5. Solubilisation by surfactants

a) Micro emulsions

b) Self micro emulsifying drug delivery system

6. Drug dispersion in carriers

a) Solid solutions

b) Solid dispersions

i. Fusion Process

ii. Solvent Method

iii. Fusion solvent

iv. Spray drying

v. Lyophilization (Spray Freeze Drying Method)

vi. Hot melt Extrusion

vii. Dropping Method

c) pH adjustment

d) Supercritical fluid process

e) Liquisolid technique

I. Chemical modification

1. Salt formation

Salt have improved solubility and dissolution characteristics in comaparison to the orignal drug .alkali metal salt of acidic drug like penicilline and strong acid salt of basic drug like atropine are more water soluble than parent drug. Ex. Aspirin, Theophylline, Barbiturates. Commercially available example of this approach is Progesterone; a water-insoluble steroid which is solubilized in peanut oil.

2. Co- crystallisation

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. Mechanism of co solvency favors the dissolution of a non-polar solute by lowering the interfacial tension. The only difference between solvates and cocrystals is the physical state of the components.

3. Co- solvency

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.

Commonly used cosolvents Glycerol, propylene glycol, PEG 400, Dimethyl Sulfoxide, Dimethyl Acetamide, Ethanol, n-Octanol are the commonly used cosolvents.[8,9]

4. Hydrotropy

Hydrotropy is unique solubilisation technique used to describe the increase in solubility of solute by the addition of large amounts of second solute result in an increase solubility of another solute.

Mechanism of action of hydrotropes

Hydrotropes are the compounds having both an anionic group and a hydrophobic aromatic ring or ring system. The hydrophilicity increase by anionic group and the ring system interacts with the solute to be dissolved. The mechanism involved in hydrotropy is related to complexation which involves interaction between lipophilic drugs and the hydrotropic agents such as urea, nicotinamide, sodium alginate, sodium benzoate etc.

Classification of hydrotropes

Table no. 03: Classification of hydrotropes.

Category	Example
Aromatic anionic	Sodium benzoate, Sodium salicylate, Sodium benzene sulphonate, Sodium benzene disulphonate, Sodium cinnamate.
Aromatic cationic	Para amino benzoic acid hydrochloride, Procaine hydrochloride, Caffeine.
Aliphatic and linear avionics	Sodium alkanoate

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, Soluplus Povacoat, dendrimers, is improving the solubility of hydrophobic API.

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

II. Physical modification: 1.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.

a) Conventional method

Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. The critical parameters of comminution are well-known to the industry, thus permitting an efficient, reproducible and economic means of particle size reduction. However, the mechanical forces inherent to comminution, such as milling and grinding, often impart significant amounts of physical stress upon the drug product which may induce degradation. The thermal stress which may occur during comminution and spray drying is also a concern when processing thermo sensitive or unstable active compounds. Also, this traditional methods are often incapable of reducing the particle size of nearly insoluble drugs (<0.1mg/mL).

b) Micronization

The process involved reducing the size of the solid drug particle 1 to 10 micron commonly by spray drying or by use of air attrition method. These processes were applied to griseofulvin, progesterone, spironolactone and disomic, fenofibrate. For each drug, Micronization improved their digestive absorption, and consequently their bioavailability and clinical efficacy.

c) Nano suspension

Nanosuspension technology has been developed as a promising candidate for efficient delivery of hydrophobic drugs. 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 stabilized by surfactants for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in Nanosuspension is usually less than one micron with an average particle size ranging between 200 and 600 nm.

There are various methods for preparation of Nanosuspension includes 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).

Advantages of nanosuspension

1. This method improves the solubility and bioavailability of drug which gives rapid onset of action.
2. To increase the bioavailability of drugs with high log P value can be formulated as Nanosuspension.
3. Dose reduction is possible.

1. Modification of the crystal habit

a) Polymorphs

b) Pseudo polymorphs

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.

2. Complexation

Complexation is the association between two or more molecules to form a non bonded entity with a well defined stoichiometry. In Complexation relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions involved.

Two type of complex available

1. **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, thereby reducing total energy of the system. Stacking can be homogeneous or mixed, but results in clear solution.
2. **Inclusion complexes:** It is formed by the inserting the nonpolar molecule or the nonpolar region of one molecule into the cavity of another molecule or group of molecules. There are no forces involved between them and therefore there are no bond is also called as no-bond complexes. Cyclodextrins are a group of cyclic oligosaccharides obtained from enzymatic degradation of starch. The three major cyclodextrins α, ß, and γ-CD are composed of six, seven, and eight D-(+) -glucopyranose units. Cyclodextrins have a hydrophilic exterior and a hydrophobic internal cavity. Cyclodextrin and their derivatives commonly use in Complexation. They form complex with drug and improve the solubility and bioavailability of poorly soluble drug. Derivatives of R-cyclodextrin with increased water solubility (e.g. Hydroxypropyl-R-cyclodextrin HP-R-CD) are most commonly used in pharmaceutical formulation.

The forces driving complexation were attributed to-

1. The exclusion of high energy water from the cavity.
2. The release of ring strain particularly in the case of –CD.
3. Van Der Wall's interactions.
4. Hydrogen and hydrophobic bindings.

Solid inclusion complexes can be prepared by using following methods

a. Kneading method

This method is based on impregnating the CDs 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.

b. Co-precipitation

In this method, in the solution of CDs the required amount of drug is added. 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.

c. Physical blending method

It is simple trituration method. In this method the CDs 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.

d. Neutralization method

In this method precipitation of inclusion compounds by neutralization technique take place. in this dissolve the drug in alkaline solutions like sodium/ammonium hydroxide and mix with an aqueous solution of CDs. The clear solution is obtained. This solution is neutralizing under agitation using hydrochloric acid solution till reaching the equivalence point. A white precipitate is being formed at this moment. This precipitate is filtered and dried.

e. Milling/Co-grinding technique

By using this method a solid binary inclusion compounds of drug and CD is prepared. In this method Drug and CDs are mixed intimately and the physical mixture is introduced in an oscillatory mill and grinded for suitable time. Ball mill is also use for preparation of binary complex.

f. 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. Lyophilisation 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. Thermo labile 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.

a) Microwave irradiation method

In this technique the microwave irradiation reaction between drug and Complexing agent takes place 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 60ºC in the microwave oven. After the reaction completes, adequate amount of solvent mixture is added to the above reaction mixture to remove the residual, uncomplexed free drug and CD. The precipitate so obtained is separated using whatman filter paper, and dried in vacuum oven at 40ºC for 48 hrs. Microwave irradiation method is a novel method for industrial scale preparation due to its major advantage of shorter reaction time and higher yield of the product.

b) Supercritical antisolvent technique

In the supercritical fluid antisolvent technique, carbon dioxide is used as anti-solvent for the solute but as a solvent with respect to the organic solvent. The use of supercritical carbon dioxide is advantageous as its low critical temperature and pressure makes it attractive for processing heat-labile pharmaceuticals. This method is important for improving bioavailability of pharmaceutically active compounds. Supercritical carbon dioxide due to its properties of improved mass transfer and increased solvating power it proved as a new complexation medium. In this technique, first, drug and CD are dissolved in a good solvent then the solution is fed into a pressure vessel under supercritical conditions, through a nozzle (i.e. sprayed into supercritical fluid anti-solvent). When the solution is sprayed into supercritical fluid anti-solvent, the anti-solvent rapidly diffuses into that liquid solvent as the carrier liquid solvent counter diffuses into the anti-solvent. Because of the supercritical fluid expanded solvent has lower solvent power than the pure solvent, the mixture becomes supersaturated resulting in the precipitation of the solute and the solvent is carried away with the supercritical fluid flow.

Solubilization by surfactants

a) Microemulsions

Micro-emulsion is the process which can dissolve the low soluble of drug. It can work to rise in the solubility of many drugs which is closely to insoluble in the aqueous form, along with mixture of proteins administration tbody. Micro-emulsion is a pure pre-concentrate manner in which it contain a hydrophilic surfactant, mixture of oil and hydrophilic solvent which can easily dissolves in soluble drug.[24] Upon the interaction with water, the preparations easily dissolve to have the clear emulsion of very minor and uniform oil droplets which contain the solubilized soluble drug. This method is isotropic, thermodynamically is steady pure systems of water, oil and surfactant, often in the combination with a co-surfactant with having a droplet size it shows the range of (20-200) nm. The homogeneous systems, which can prepared with the extensive range of the surfactant concentration, in oil and water all fluids of low viscosity. The major drawback of micro-emulsions their have greater concentration of co-surfactant/surfactant, which making them unsuitable for intravenous admin. Below the critical micelle concentration and having the dilution of micro-emulsions of the surfactants cause precipitation of the drug; however, the fine particle size resulting the precipitate which would still improve absorption. Advantage of micro emulsions it can easily manufacture and have the optimal bioavailability.

b) Self micro emulsifying drug delivery system

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 micro emulsifying drug delivery systems (SMEDDS) are isotropic solutions of oil and surfactant which form oil-in-water micro emulsions on mild agitation in the presence of water. These novel colloidal formulations on oral administration behave like oil-in-water micro emulsions.

Composition of SEDDS[27]

The composition of self emulsifying system is simple combination of drug, oils, surfactant and co surfactant or co-solvent. The self-emulsifying process depends on:

The nature of the oil and surfactant The concentration of surfactant The temperature at which self emulsification occurs

1. **Oils:** Oils can Solubilized the lipophilic drug in a specific amount. Oil can facilitate self-emulsifying and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, increasing absorption from GIT. Example; olive oil, oleic oil, sesame oil.
2. **Surfactant:** Non-ionic surfactant with high hydrophilic-lipophilic balances (HLB) value is used in the formulation of SEDDS. High HLB and hydrophillicity of surfactant assists the immediate formulation of o/w droplets and rapid spreading of formulation in the aqueous media. Example; Tween, Labrasol, Labrafac CH 10, cremophore etc.
3. **Co-surfactant/ co-solvent:** Dissolve large amount of hydrophilic surfactant or hydrophobic drugs in lipid phase. It increases fluidity of the interfacial film. Example: ethanol, propylene glycol, polyethylene glycol, polyoxyethlene, propylene carbonate tetrahydrofurfuryl alcohol, Glycofurol etc.

Drug dispersion in carriers

a) Solid solutions

Solid solutionis 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.

c) Solid dispersions

In 1961, Sekiguchi and Obi first introduce the solid dispersions to increase the dissolution and oral absorption of poorly water-soluble drugs.

In solid dispersion a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which enhances the dissolution of the drug which can yield eutectic (non-molecular level mixing) or solid solution (molecular level mixing) products.

Advantages of solid dispersion

1. Reduction in particle size: different carrier use in solid dispersion reduces particle size of drug particle which improve solubility and bioavailability.
2. Improve wettability of particle: solid dispersion improves wettability of particle.

3. Improve porosity: Solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore, result in a higher dissolution rate
4. Improve dissolution which ultimately improves the solubility and bioavailability.

Disadvantages of solid dispersion

1. Instability due moisture content.
2. Difficulty in incorporating into formulation of dosage forms.

Polymers used in solid dispersions

Polyethylene Glycol (PEG)

The term polyethylene glycol refers to compounds that are obtained by reacting ethylene glycol with ethylene oxide. PEGs whose molecular weight is above 300000 are commonly termed as polyethylene oxides30

Phospholipids

The complexity of glycerides advances by modification of the terminal hydroxyl with phosphate linked head groups to form phospholipids, common phospholipid head groups include choline, ethanolamine, serine, inositol and inositol phosphate, and glycerol esters. As with the triglycerides, numerous species are possible by various combinations of different head groups and fatty acyl substitution at the first and second positions of the glycerol backbone, fluidity differences are evident as a function of the gel to liquid crystalline transition temperatures. Solubility of phospholipids is intimately linked to the confirmation of the aggregate material rather than strictly a chemical function of the molecule. Monodactyl phospholipids, which tend to form micelles, are usually more readily soluble in aqueous solutions

Polyvinyl Pyrrolidone (PVP)

PVP has a molecular weight ranging from 10000 to 700000. It is soluble in solvents like water, ethanol, chloroform and isopropyl alcohol. PVP is not suitable for preparation of solid dispersions prepared by melt method because of its melt at a very high temperature above 275, where it becomes decomposed.

Effect of PVP Molecular Weight

The effect of molecular weight of PVP on the rate of dissolution of a drug is more consistent than for PEG. An increase in molecular weight of PVP will decrease the dissolution rate of most drugs.[30] An increase in viscosity of PVP solution due to an increase in molecular weight decreases diffusion of drug molecules from the surface of viscous material into the dissolution medium, lower molecular weight PVP has a short swelling time prior to dissolution resulting in an increase in dissolution n rate of the polymer and drug.

Cyclodextrins

Cyclodextrins are primarily used to enhance solubility, chemical protection, taste masking \and improved handling by the conversion of liquids into solids by entrapment.

Advantages of cyclodextrins

1. Increasing the stability of the drug
2. Release profile during gastrointestinal
3. Transit through modification of drug
4. Release site and time profile.
5. Decreasing local tissue irritation.
6. Masking unpleasant taste.

Methods of preparation of solid dispersion

i) Melting method

The melting or fusion method, first proposed by Sekiguchi and Obi involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. Appropriately this has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures.

ii) Solvent method

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents.

However, some disadvantages are associated with this method such as

1. The higher cost of preparation.
2. The difficulty in completely removing liquid solvent.
3. The possible adverse effect of traces of the solvent on the chemical stability
4. The selection of a common volatile solvent.
5. The difficulty of reproducing crystal form.
6. In addition, a super saturation of the solute in the solid system cannot be attained except in a system showing highly viscous properties.

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 Thermo labile.

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)

Freezing of drugs solution in cryogenic fluid vapours and subsequent removal of frozen solvent produces fine drug particles with high wettability. During SFV/L the atomized droplets typically start to freeze in the vapor phase before they contact the cryogenic liquid. As the solvent freezes, the drug becomes supersaturated in the unfrozen regions of the atomized droplet, so fine drug particles may nucleate and grow.

vi) Hot melt extrusion

The drug/carrier mix is typically processed with a twin-screw extruder. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermo labile to be processed. Solid dispersion by this method is composed of active ingredient and carrier, and prepare by hot-stage extrusion using a co-rotating twin-screw extruder. The concentration of drug in the dispersions is always 40% (w/w). The screw-configuration consist of two mixing zones and three transport zones distribute over the entire barrel length, the feeding rate is fix at 1 kg/h and the screw rate is set at 300 rpm. The five temperature zones are set at 100, 130, 170, 180, and 185C from feeder to die. The extrudates are collect after cooling at ambient temperature on a conveyer belt. Samples are milled for 1 min with a laboratory-cutting mill and sieve to exclude particles >355µm.

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.

III. pH adjustment

These can be achieved by two ways – in situ salt formation and addition of buffer to the formulation. PH is required for the solubility of drug more ionic drug can easily solubilize. PH is main parameter of drug to maintain the solubility and for the purposed of pharmacological response. PH is required for the purposed of administration of drug. The drug having low solubility can precipitate in the blood it cannot soluble in the blood because blood has acidic in nature which effect in the blood. The suitable PH should require for the absorption of drug. PH of stomach is 1 -2 and duodenum is 5-6 the degree of solubility is responsible to pass to body. This method is used regularly used examination as preclinically for pH adjustment. It is a new method to measure efficiency of the low soluble drugs.

Advantage of this method is simple to formulate the formulation and uses of small quantity for the evaluation e.g. buffer aspirin tablet.

IV. Supercritical fluid process

Super critical fluid is fluid which exists as single fluid above its critical temperature and pressure. SCF shows the properties of both a liquid and a gas above its critical condition. It is safe, environmentally friendly, and economical. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research. At near-critical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power.

Process is having the low operating condition and also they can recrystallize and can reduce the particle size. Precipitation by infusion or impregnation of the polymers with bioactive product, Antisolvents, Compressed Fluid, and Solution improved Dispersal by the Supercritical Fluid techniques.

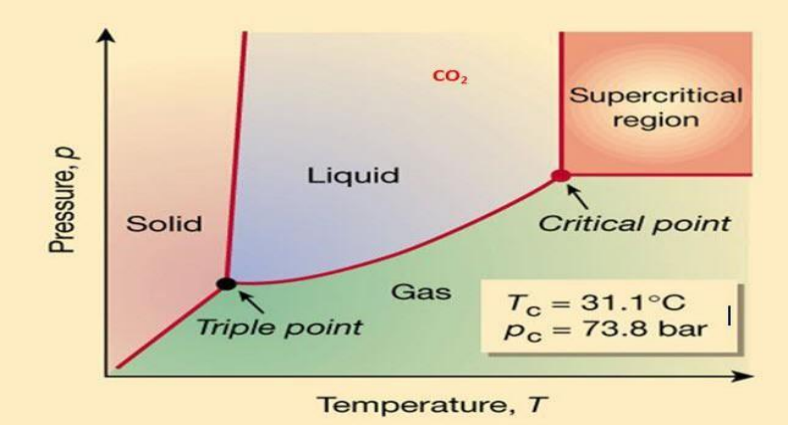

Figure 02: Phase diagram of super critical fluid.

V. Liquisolid technique

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.

CONCLUSION

For orally administered drugs solubility is one of the rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Recently more than 40% NCEs (new chemical entities) developed in Pharmaceutical Industry are practically insoluble in water. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. To overcome the solubility problem various solubility enhancement methods are develop today which is Various technique of Traditional such as PH, Particle Size Distribution, Solvency, Micro-emulsion Complexation, Micellar Solubilization, Supercritical fluid process, Solid dispersion, Hydro trophy. And Nowadays the Advance techniques are Micronization, Nano-suspension, and Homogenization, Salt formation, Spray Drying, Solvent Evaporation, Hot-melt Extrusion, and Conventional method for solid dispersion etc. By using newer techniques which are discussed above it is possible to improve solubility of poorly water soluble drugs.

REFERENCES

1. Rinaki E, Valsami G, and Macheras P; Quantitative Biopharmaceutics Classification System; the central role of dose/solubility ratio. *Pharm. Res*, 2003; 20: 1917.
2. Indian pharmacopoeia, Government of India ministry of health and familywelfare, published by the government of publication, Delhi, 2014.
3. Sinko, P.J, *Martin's Physical pharmacy and pharmaceutical science*, Wolters kluwer, New Delhi, 2011.
4. Wu, C.Y., Benet, L.S., *Pharmaceutical research*, 2005*; 22(1):* 23-27.
5. Aggarwal S., Gupta G.D.,and Chaudhary S., Solid dispersion as an eminent strategic approach in solubility enhancement of poorly soluble drugs. International Journal of Pharmaceutical Sciences and Research, Wu C.Y., Benet L.S., Predicting drug, 2010; 1: 1-13.
6. Serajuddin, A.T, *Adv Drug Deliv Rev*, 2007; *59(7):* 603-16.
7. Patole, T., Deshpande, A., *Int J Pharm Sci Res*, 2014; *5(9):* 3566-3576.
8. Chaudhary, A., Nagaich, U., Gulati, N., Sharma, V. K., Khosa, R. L., *J AdvPhar Edu Res*, 2012; *2(1).*
9. Vemula, V. R., Lagishetty, V., Lingala, S., *Int. J Pharm Sci Rev Res*, 2010; *5(1): 41-51*.

10. Vemula, V. R., Lagishetty, V., Lingala, S., *Int. J Pharm Sci Rev Res*, 2010; *5(1): 41-51*.
11. Nidhi K., Indrajeet S., Khushboo M., Gauri K., Sen D.J., Hydrotropy: a promising tool for solubility enhancement. International Journal of Drug Development and Research, 2011; 3(2): 26-33.
12. Sharma, M., Sharma, R., Jain, D. K., *Scientifica*, 2016.
13. Adam M Persky and Jeffrey A Hughes; Solutions and Solubility. http://www.cop.ufl.edu/safezone/prokai/ pa5100 /pha5110.htm
14. Blagden N, Gavan P T, York P; Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates, *Adv. Drug Del. Rev*, 2007; 59(30): 617-630. 33.
15. Aulton M E, Pharmaceutics: The science of dosage form design, London: Churchill Livingstone, 2002; 2: 113-138.
16. Dubey R; Pure drug nanosuspensions impact of nanosuspension technology on drug discovery and development. *Drug Del. Tech*, 2006.
17. Muller R H, Jacobs C and Kayer O; Nanosuspensions for the formulation of poorly soluble drugs. In: F Nielloud, G Marti-Mestres (ed). Pharmaceutical emulsion and suspension. New York, Marcel Dekker, 2000; 383-407.
18. Nash R A; Suspensions. In: J Swarbrick, JC Boylan (ed). Encyclopedia of pharmaceutical technology. Second edition New York, Marcel dekker, 2002; 2045-3032.
19. Patravale V.B., Date A.A., Kulkarni R.M., Nanosuspension: a promising drug delivery strategy. Journal of Pharmacy and Pharmacology, 2004; 56: 827-840.
20. Vippagunta S.R., Zaren W., Hornung S., Krill S.L., Factors affecting the formation of eutectic solid dispersions and their dissolution behaviour. Journal of Pharmaceutical Science, 2006; 96: 230 – 294.
21. Loftsson T., Brewster M.E., Pharmaceutical applications of cyclodextrins: drug solubilisation and stabilization. Journal of Pharmaceutical Science, Patil J.S., Kadam D.V., 1996; 85: 1017-1025.
22. Patil J.S., Kadam D.V., Marapur S.C., Kamalapur M.V., Inclusion complex sytem. A ovel techniques to improve the solubility and bioavailability of poorly drug: a Review. International journal of pharmaceutical sciences, 2010; 2(2): 29-34.
23. Charoenchaitrakool M., Dehghani F., Foster N.R., Utilization of supercritical carbon dioxide for complex formation of ibuprofen and methyl- betacyclodextrin. International Journal of Pharmaceutics, 2009; 239: 103-112.

24. M. Singh, A. Sayyad, and S. Sawant, "Review on various techniques of solubility enhancement of poorly soluble drugs with special emphasis on solid dispersion," J Pharm Res, 2010; 3, 10: 2494501.
25. S. Jain, N. Patel, and S. Lin, "Solubility and dissolution enhancement strategies: current understanding and recent trends," Drug development and industrial pharmacy, 2015; 41, 6: 875887.
26. P. Gowardhane, N. V. Kadam, and S. Dutta, "Review on enhancement of solubilizationprocess,"American Journal of Drug Discovery and Development, 2014; 4, 2: 134-152.
27. Gordon L Amidon, John R Crison. Methods and formulation for increasing the bioavailability of poorly water-soluble drugs. US Patent, 1999; 5993858: 30.
28. Arora S.C., Sharma P.K. et al., Development, characterization and solubility study of solid dispersion of cefiximetrihydrate by solvent evaporation method. International Journal of Drug Development & Research, 2010; 2: 424-430.
29. Price JC. Polyethylene glycol. In: Wade A, Weller PJ, Ed. Handbook of Pharmaceutical Excipients, Washington DC/London: American Pharmaceutical Association/The Pharmaceutical Press, 1994; 355361.
30. Shah JC, Chen JR, Chow D, Preformulation study of etoposide, increased solubility and dissolution rate by solid-solid dispersions, Int J Pharm, 1995; 103-111.
31. Serajuddin A. Solid Dispersion Technique. J. Pharm. Sci, 1999; 88(10): 891-90
32. Narang A, Shrivastava A. Drug Dev. Ind. Pharm, 2002; 26(8): 111-115.9.
33. Buxton I R and Peach J M; Process and apparatus for freezing a liquid medium US4470202, 1984.
34. Pawar, A.R., Choudhari, P.D., *Asian J. Biomed. Pharm. Sci*, 2012; *13:* 9-14.
35. S. Jatwani, A. C. Rana, G. Singh, and G. Aggarwal, "An overview on solubility enhancement techniques for poorly soluble drugs and solid dispersion as an eminent strategic approach," Int. J. Pharm. Sci. Res, 2012; 3, 4: 942-956.
36. Subramaniam B., Rajewski R. A., Snavely K., Pharmaceutical processing with supercritical carbon dioxide. Journal of pharmaceutical science, 1997; 86: 885-890.
37. Pardhi, D., Shivhare, U., Suruse, P., Chabra, G., *Res J Pharm Dosage FormsTech*, 2010; *2(5):* 314322.