DRUG SOLUBILITY: IMPORTANCE AND ENHANCEMENT TECHNIQUES

First Author[1] : Vikas Vijay Saper, Second Author[2] : MR. Ghugarkar Prasad Gorakshanath
1(Student, SPPU Of Pune , DR.N.J.Paulbudhe College Of Pharmacy, Shanishwar Nagar, Vasant Tekdi Ahmednager-41400 Email; Vikassapre72@Gmail.Com)
2(Department Of Pharmaceutics, SPPU Of Pune, DR.N.J. Paulbudhe College Of Pharmacy, Shanishwar Nagar, Vasant Tekdi Ahmednager-41400 Email:)

1. Abstract:

The solubility process is ability to amount of solute which is dissolved in the solvent to form a solution below a particular situation of gravity and temperature. Solubility plays a vital-role in the dissolution procedure to complete a movement for required response and solubility of drug for the purpose of better bioavailability. Solubility is the parameter to achieve desired concentration of drug for pharmacological response in systemic circulation. A poorly water-soluble drug is requiring high doses in order to reach therapeutic plasma concentrations after oral administration. According to the Biopharmaceutics Classification system class II of drugs amount preventive step in which the drug released from dosage form and solubility in stomach fluid and not having the absorption, so when its rises solubility which is turns into rises bioavailability for BCS class II of drugs drug shows parameter of the solubility and permeability of the drug. Method of different solubility enhancement techniques is physical, chemical modification and other techniques etc. The different technique of Traditional such as PH, Particle Size Distribution, Co-solvency, Micro-emulsion Complexation, Micellar Solubilization, Supercritical fluid process, Solid dispersion, Hydro trophy. And Nowadays the Advance techniques are like as Particle size, Nature of solute and solvent, Temperature, Pressure, Polymorphs, and Ph. Having the Greater surface have greater dissolution rate. Therefore, if the area is rises with falling in the size of particle which can be skilled for the predictable methods as like example ball milling, trituration, grinding fluid energy micronization, controlled precipitation and salt formation. Hence, design approaches are being exposed to improve bioavailability of the drugs. This article aims is to describe the different solubility enhancement techniques to improve the solubility of the drug by different approach like Advanced and traditional methods. Micronization, Nano-suspension, and Homogenization, Salt formation, Spray Drying, Hot melt Extrusion, Solvent evaporation, and Conventional technique for solid dispersion. Factor affecting solubility etc.

Key words: Solubility enhancement, Traditional and advance method, BCS classification, Dissolution

2. Introduction:

The solubility is process ability to amount of the solute which is dissolved in the solvent to form a solution below a particular situation of gravity and temperature [1]. Solubility plays a vital role in dissolution procedureto complete a movement for required pharmacological response and solubility of drug purpose for better bioavailability. Solubility Enhancement Techniques is the additional useful techniques for the Formulation procedure. Solubility is the unique concept of any Physical and Chemical including the Pharmacokinetics therapy which is more useful in consideration of medicine and Biopharmaceutical [2]. Solubility enhancement technique for determination of the solubilization of drug which contains like Micronization, solid dispersion, PH adjustment, Micellar solubilization, co-solvency Complexation, hydrotropic [3]. Furthermore, solubility enhancement technique is distinguishing as a physical modification and the chemical modification of the Drug substance for the purpose of the checking parameter of the solubility of the drug. This technique is used for the improvement of solubility, dissolution for the oral, parenteral drug administration [4]. Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution. the solvent is generally a liquid, which can be a pure substance or a mixture of two liquids. One may also speak of solid solution, but rarely of solution in a gas. The extent of solubility ranges widely, from infinitely soluble (fully miscible) such as ethanol in water, to poorly soluble, such as silver chloride in water. The term insoluble is often applied to poorly or very poorly soluble compounds The different technique of Traditional such as PH, Particle Size Distribution, Co-solvency, Micro-emulsion Complexation, Micellar Solubilization, Supercritical fluid process, Solid dispersion, Hydro trophy. And Nowadays the Advance techniques are like as Micronization, Nano- suspension, and Homogenization, Salt formation, Spray Drying, Hot melt Extrusion, Solvent evaporation, and Conventional technique for solid dispersion [5].

3. Importance:

For purpose of the absorption is most suitable and common employed for the path of drug delivery. In line for simplicity of management, high patient compliance, rate effectiveness, smallest sterility restraints, and its flexibility in the modified dosage form. Maximum of the drugs like pharmacologic reaction can be linked directly to plasma levels of drug which show the result in the drug to the body [6]. Bioavailability can determine the better solubility of drug and how it's showing the pharmacological response. Solubility is the key parameters to found out meditation of drug in complete movement to doing required pharmacological response to a particular drug. Any drug which is administered drug or to be fascinated must be existing in the aqueous solution in from of location the absorption which can easily show the response to the site of action. Liquid is the maximum common using solvent for the liquid pharmaceutical formulations or in any solubility process. The drugs having the weakly acidic or weakly basic have a poor aqueous solubility. Development of drug solubility in its bioavailability which is remains unique and interesting/challenge parts of drug development procedure and solubility of drug it's important for drug delivery system [7]. The lower solubility drug and lower dissolution rate of the poorly water-soluble drugs in aqueous stomach liquids frequently that reason of inadequate bioavailability. According to the Biopharmaceutics Classification system class II of drugs rate preventive step in which the drug released from dosage form and solubility in stomach fluid and not have the absorption, so when it rises the solubility which is turns into rises bioavailability for BCS class II of drugs. BCS drug shows the parameter of solubility and permeability of the drug [8]. Having the Greater surface area and have greater dissolution rate. Therefore, if the area is riseswith falling in the size of particle which can be skilled by the predictable methods as like example ball milling,trituration, grinding fluid energy micronization, controlled precipitation and salt formation. Hence, design approaches are being exposed to improve bioavailability of the drugs [9].

Different method of solubility enhancement is given below:

Physical modification
Chemical modification
and other techniques [10]

4. Physical Investigation Change's:

a. Size reduction: Micronization, Homogenization, Nanosuspension, Supercritical fluid process, and Spray drying etc.
b. Crystal habit change: Polymorphs and pseudo-polymorphs
c. Drug dispersion in the carrier: Eutectic mixture, Hot plate process, Solvent evaporation process, Melting Solvent process
d. Complex action: Molecular complexes, Chelates, Inclusion, Inorganic coordination
e. Solubilization by surfactant: Micro-emulsion
f. Chemical identification: Salt formation
g. Other techniques: Co-Crystallization, co-solvency, Solubilizing agents [1,7,10,11]

The solubility having a grade of ion and by what method and once mixing by other ion that can be led to or remain aqueous Solubility balance is a dynamic equilibrium that effects when it have a chemical on balance with a solution of those compounds. According to the drug with low aqueous solubility or class II or uniform class IV compounds of BCS were present in dissolution connected to the absorption problem [4].

5. Solubility Expression:

Classification	Volume of solvent required to dissolve 1gm/ml drug
Very soluble drug	Less than 1
Free soluble drug	From 1-10
Soluble drug	From 10-30
Sparingly soluble drug	From 30-100
Slightly soluble drug	From 100-1000
Very slightly soluble drug	From 1000-100000
In-soluble drug	Greater than 100000 [12]

Table No 1 Solubility Expression

6. Method of Solubilization:

Process 1: Its shows the breakage of interionic or bond form intermolecular in the solute parting molecule in solvent which provide space in the solvent for interaction of solute among the solute particle for ion and solvent.
Process 2: The particle of solid which break the particles which is away from the bulk substances.
Process 3: And solid molecules is combined with the solvents [13,14]

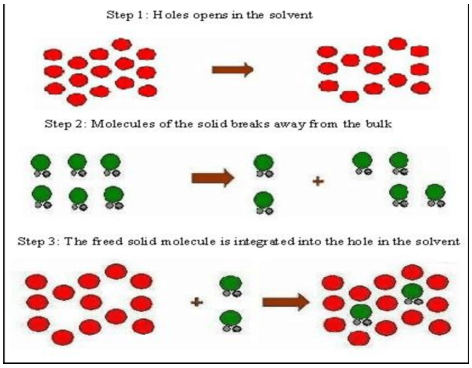

fig. no 1 method of solubilization

7. Bio-Pharmaceutics classification system (BCS):

It is classify in four classes according to the solubility and permeability showing different nature of the drug [15].

Class	Permeability		Solubility	Example
I	High Permeability		High Solubility	Propranolol, diazepam, Acyclovir, Levodopa, Metoprolol
II	High Permeability		Low Solubility	Nifedipine, Naproxen, Amlodipine, Itraconazole
III	Low Permeability		High Solubility	Cimetidine, Nephazolin, Metformin
IV	Low Permeability		Low Solubility	Taxol, Clorthiazol, Colistin

Table 2: BCS with example

8. Factors Affecting Solubility:

- **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

- **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 increasingtemperature.

- **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 [7].

- **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 [1,16].

9. Techniques of Solubility Enhancement:

A. 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 greater interaction with the solvent which causes an increase in solubility. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. Particle size reduction is thus permitting an efficient, reproducible, and economic means of solubility enhancement [17]. 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 thermos sensitive or unstable activecompounds. Using traditional approaches for nearly insoluble drugs may not be able to enhance the solubility up to desired level. Micronization is another conventional

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

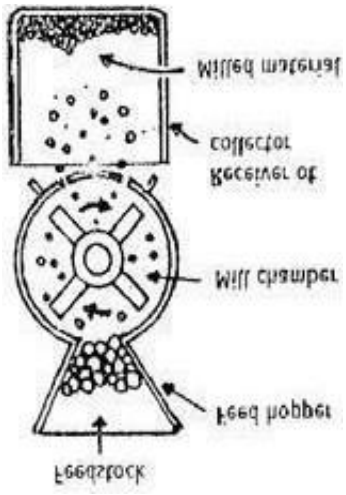

Fig.2 Particle Size Reduction

B. Nanonization:

Recently, various nanonization strategies have emerged to increase the dissolution rates and bioavailability of numerous drugs that are poorly soluble in water. Nanonization broadly refers to the study and use of materials and structures at the nanoscale level of approximately 100 nm or less. Nanonization can result in improved drug solubility and pharmacokinetics, and it mightalso decrease systemic side-effects for many new chemical entities with very low solubility, oral bioavailability enhancement by micronization is not sufficient because micronized product has the tendency to agglomerate, which leads to decrease effective surface area for dissolution, the next step is nanonization. There are different techniquesused for nanonization of drug including Wet milling, Homogenization, Emulsification-solvent evaporationtechnique, Pear milling, Spray drying etc. There are many examples of nanonization of drugs [21,22].

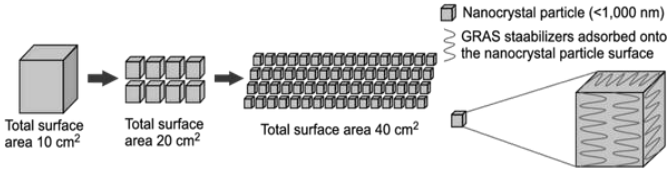

Fig. no 3 Nanonization

C. Cosolvency:

The solubility of poorly soluble drugs in water can be increased by mixing it with some water miscible solvent in which the drug is readily soluble. This process is known as cosolvency and the solvent used in combination are known as cosolvent. Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly known as solvent blending. There is a dramatic change in the solubility of drugs by addition of organic co-solvent into the water. The cosolvents are having hydrogen acceptor or donor groups with a small hydrocarbon region. The hydrophobic hydrocarbon region usually interferes with the hydrogen bonding network of water which consequently reduces the intermolecular attraction of water while the hydrophilic hydrogen bonds ensure water solubility [23].

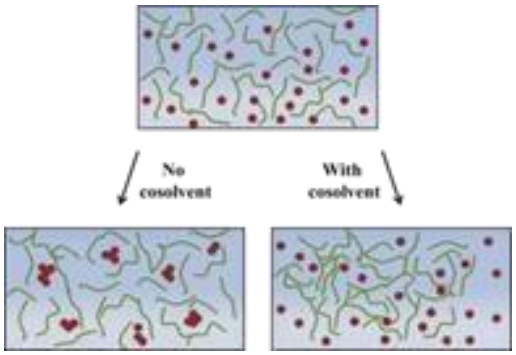

Fig. no 4 Cosolvency.

D. Hydrotropy:

Hydrotropy is a volatilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of existing solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water-soluble drugs.

E. PH Adjustment:

Poor water-soluble drug may potentially dissolve in water by applying a pH change. To access the solubility of this approach, the buffer capacity and tolerability of the selected

pH is 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 [24].

F. Sonocrystallisation:

Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employedsuccessfully to reduce particle size. The novel approach for particle size reduction on the basis of crystallization by using ultrasound is Sonocrystallisation. Sonocrystallisation utilizes ultrasound power characterized by a frequency rangeof 20-100 kHz for inducing crystallization. It's not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients. Most applications use ultrasound in the range 20 kHz-5 MHz [25].

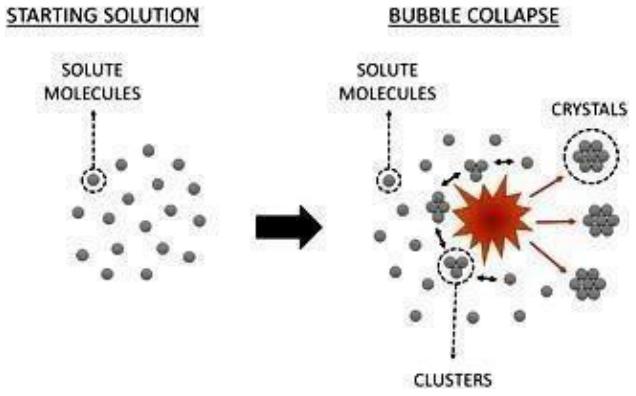

Fig.no 5 Sonocrystallisation

G. Supercritical Fluid (Scf) Process:

The number of applications and technologies involving supercritical fluids has also grown explosively. It has been known for more than a century that supercritical fluids (SCFs) can dissolve nonvolatile solvents, with the critical point of carbon dioxide, the most widely used supercritical fluid. It is safe, environmentally friendly, and economical. The low operating conditions (temperature and pressure)make SCFs attractive for pharmaceutical research [26]. A SCF exists as a single phase above its critical temperature (Tc) and pressure (Pc). SCFs have properties useful to product processing because they are intermediate between those of pure liquid and gas (i.e., liquid-like density, gas-likecompressibility and viscosity and higher diffusivity than liquids). Moreover, the density, transport properties (such as viscosity and diffusivity), and other physical properties (such as dielectric constant and polarity) vary considerably with small changes in operating temperature, pressure, or both around the critical points [27] Hence, it is possible to fine-tune a unique combination of properties necessary for a desired application. These unique processing capabilities of SCFs, long recognized and applied in the food industry, have recently been adapted to pharmaceutical applications. Commonly used supercritical solvents include carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water. Once the drug particles are solubilized within SCF, they may be recrystallized at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows micronization of drug particles within narrow ranges of particle size, often to sub- micron levels. Current SCF processes have demonstrated the ability to create nano suspensions of particles 5-2,000nm in diameter. Several pharmaceutical companies, such as Nektar Therapeutics and Lavipharm, are specializing in particle engineering via SCF technologies for particle size reduction and solubility enhancement. Several methods of SCF processing havebeen developed to address individual aspects of these shortcomings, such as precipitation with compressed antisolvents process (PCA), Rapid Expansion of Supercritical Solutions, Gas Antisolvent Recrystallization, Precipitation with Compressed Fluid Antisolvent, Impregnation or infusion of polymers with bioactive materials, Solution enhanced Dispersion by Supercritical Fluid, solution enhanced dispersion by SCF (SEDS), supercritical antisolvents processes (SAS) and aerosol supercritical extraction system (ASES)

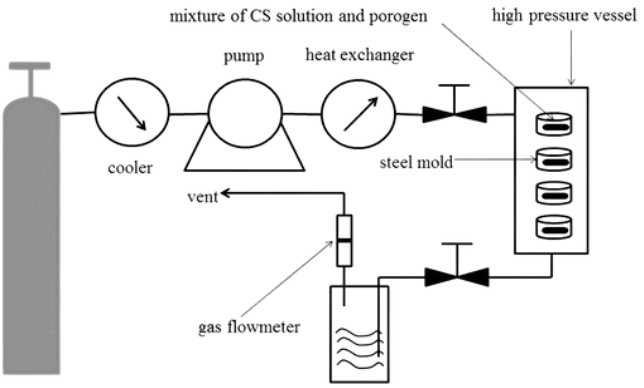

Fig.no 6 supercritical fluids

H. **Solid Dispersion:**

The concept of solid dispersions was originally proposed by Sekiguchi and Obi, who investigated the generation and dissolution performance of eutectic melts of a sulfonamide drug and a water-soluble carrier in the early 1960s [28]. Solid dispersions represent a useful pharmaceuticaltechnique for increasing the dissolution, absorption, and therapeutic efficacy of drugs in dosage forms. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone (Povidone, PVP), polyethylene glycols (PEGs), Plasdone-S630. Surfactants like Tween-80, docusate sodium, Myrj-52, Pluronic-F68, and sodium lauryl sulphate (SLS) also find a place in the formulation of solid

dispersion. The solubility of celecoxib, halofantrine, and ritonavir can be improved by solid dispersion using suitable hydrophilic carriers like celecoxib with povidone (PVP) and ritonavir with gelucire. Various techniques to prepare the solid dispersion of hydrophobic drugs with an aim to improve their aqueous solubility are listed [29]

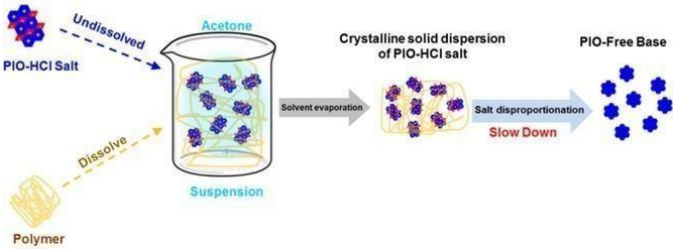

Fig No 7 Solid dispersion

a. Fusion Process:

In the fusion method of preparation, 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. Several mechanisms could operate during the process of dispersion. If the drug has a high degree of solubility in the carrier, the drug could remain ―dissolved‖ in the solid state, yielding what is known as a solid solution.Particle size reduction under these conditions proceeds to the ultimate level leading to molecular dispersion of the drug in the carrier matrix. These systems show very high drug dissolution rates compared to control samples. If, on the other hand, the solubility of the drug in solid state is not so high, crystallites of the drug become dispersed in the matrix. Such systems show only moderate increases in dissolution rates [30].

b. Solvent Method:

In the solvent method of preparation, 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 coprecipitate is then dried under vacuum to drive out any solvent freely adhering to the particle surface. However,there is a possibility of the formation of a solvate within the crystal lattice. This presents a problem in terms of pharmaceutical acceptance since most of the solvents used are non-aqueous (organic) and toxic. Hence, removal of even trace amounts of the solvent is implied. Highly sensitive techniques such as differential scanning calorimetry (DSC), differential thermal analysis (DTA), thermogravimetric analysis (TGA), and less sensitive procedures like gravimetry and spectroscopy can be used to demonstrate complete solvent removal [31].

c. Fusion-Solvent Method:

In the fusion methods a 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. Otherwise, this method faces the same criticism of solvent retention described before. This method is particularly useful for drugs that have high melting points or that are thermolabile. The feasibility of the method has been demonstrated for spironolactone and griseofulvin dispersions in polyethylene glycol 6000 [31].

d. Spray Drying:

In this type of preparation, the carrier and the active ingredient are dissolved or 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 [32].

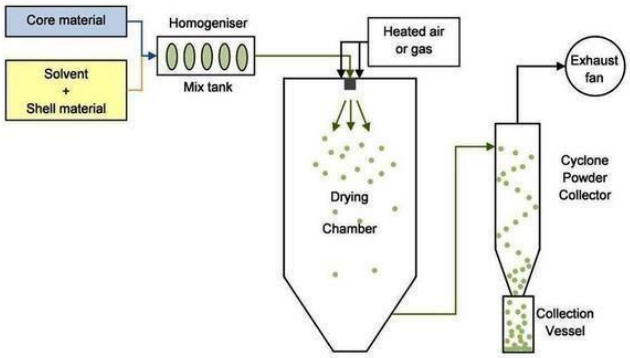

Fig. no 8 Spray Drying.

e. Lyophilization (Spray Freeze Drying Method):

This method is used to avoid the heating during the preparation of thermosensitive drugs; spray freeze drying (SFD) has been successfully developed to prepare solid dispersions at ambient temperature, which was made significant development by the research work of William III. 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 [33-35]

f. Hot-melt Extrusion:

It is a very common method used in the polymer industry. But Speier and Hutten Rach 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 [29]

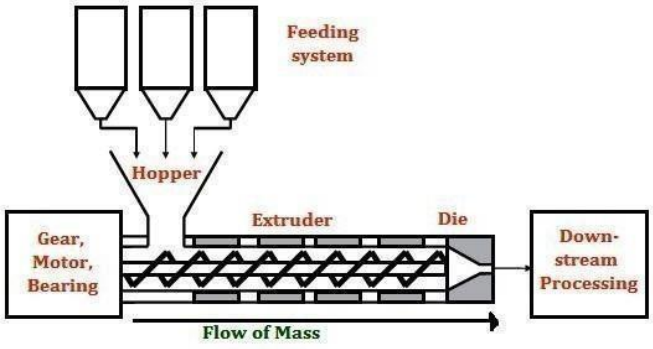

Fig. no 9 Hot –Melt Extrusion

I. Inclusion Complexation:

Among all the solubility enhancement techniques, inclusion complex formation technique has been employed more precisely to improve the aqueous solubility, dissolution rate, and bioavailability of poorly water-soluble drugs. Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The major structural requirement for inclusion complexation is a snug fit of the guest into the cavity of host molecule. The cavity of host must be large enough to accommodate the guest and small enough to eliminate water, so that the total contact between the water and the nonpolar regions of the host and the guest is reduced. Various techniques are used to prepare for making inclusion complexes of poor soluble drugs with an aim to improve their aqueous solubility are listed [36].

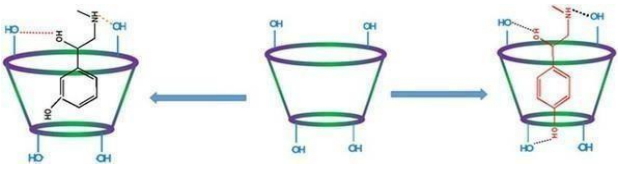

Fig. no. 10 Inclusion Complexations

a. Kneading:

The method involves the formation of paste of cyclodextrin with guest molecules by using small quantity of either water or ethanol to form kneaded mass. Kneaded mass can be dried at 45 °C and pulverized [37].

b. Melting:

Excess quantity of guest melted, mixed with powdered cyclodextrin, after cooling excess quantity of quest is removed by washing with weak complex forming solvent. The method restricted to sublimable guest like menthol [37].

c. Solution-enhanced Dispersion by the Supercritical fluids (SEDS):

SEDS is novel, single step method, which can produce solid drug-cyclodextrin complexes. The optimization of processing conditions is essential in order to achieve the optimum complexation efficiency and to compare with drug-cyclodextrin complexation methods described earlier in the literature (e.g., kneading, freeze drying, spray drying etc.).
Advantages over other methods are
Preparation of solid-cyclodextrin complexes in single step process,
Achievement of high complexation efficiency (avoidance of excess cyclodextrin in powder).
Possibility to minimize the contact of drug with cyclodextrin during the process.
Achievement of enhanced dissolution rate of the drug (which is comparable to the dissolution behavior of micronized drug-cyclodextrin complex) [37].

d. **Co-evaporation/Solvent Evaporation Method:**

To the alcoholic solution of guest, aqueous solution of host is added and stirred for sometimes and evaporated at room temp until dried mass obtained, pulverized and sieved and fraction is collected [37].

e. Microwave Irradiation:

This method is developed for rapid organic synthesis and reactions, which require shorter reaction time and higher aim product [37].

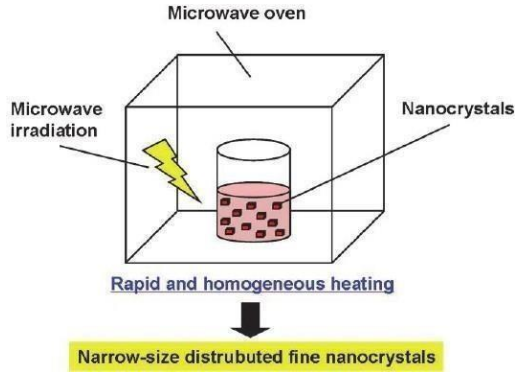

Fig. no 11 Microwave Irradiation

f. Freeze Drying / /Lyophilization Technique:

The required stoichiometric quantity of host and guest were added to aqueous solution of cyclodextrin and this suspension stirred magnetically for 24 hours, and resulting mixture is freeze dried at 60 °C for 24 hours [37].

g. Spray Drying/Atomization:

In this method, host solution prepared generally in ethanol: water 50% v/v. To this guest is added and resulting mixture is stirred for 24 hr. at room temperature and solution is spray dried by observing following conditions-air flow rate, atomizing air pressure, inlet temperature, outlet temperature, flow rate of solution etc. Product obtained by passing through 63-160 micrometer granulometric sieve [37].

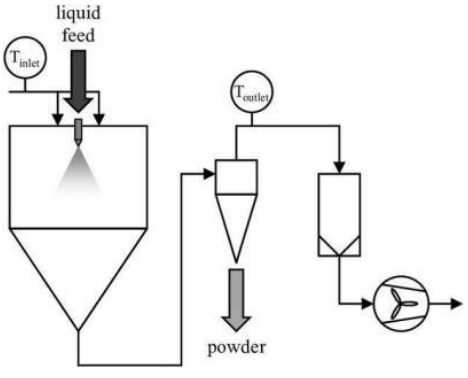

Fig. no. 12 Spray Drying

J. Self-Emulsifying or Self-Micro Emulsifying Systems:

Self-emulsifying or self-micro emulsifying systems use the concept of in situ formation of emulsion in the gastrointestinal tract. The mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvents and co-solvent forms a transparent isotropic solution that is known as the self- emulsifying drug delivery system (SEDDS), in the absence of external phase (water) and forms fine o/w emulsions or micro-emulsions spontaneously upon dilution by the aqueous phase in the GIT and is used for improving lipophilic drug dissolution and absorption. The ease of emulsification could be associated with the ease of water penetrating into the various liquids crystalline or gel phases formed on the surface of the droplet. One of the advantages of SEDDS in relation to scale up and manufacture is that they form spontaneously upon mixing their components under mild agitation and they are thermodynamically stable. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations. The large quantity of surfactant in self-emulsifying formulations (30- 60%) irritates GIT. Most self- emulsifying systems are limited to administration in lipid filled soft- or hard-shelled gelatin capsules due to the liquid nature of the product. Interaction between the capsule shell and the emulsion should be considered so as to prevent the hygroscopic contents from dehydrating or migrating into the capsule shell. A Neoral-R is an example of selfmicroemulsfying drug delivery system (SMEDDS). Depending on the dose level, the relative bioavailability of cyclosporine-α administered. A Neoral-R could be 174-239% of the bioavailability of cyclosporine-α from Sandimmune-R, the originally marketed formulation. Emulsion droplet size is a major factor influencing bioavailability of drugs from emulsion formulations, with small droplet radii enhancing the plasma levels of drugs, in part due to direct lymphatic uptake. Since SMEDDS contain high concentration of surfactants, they should be limited to oral applications and may not be advisable for long term use due to the potential of causing diarrhea [37].

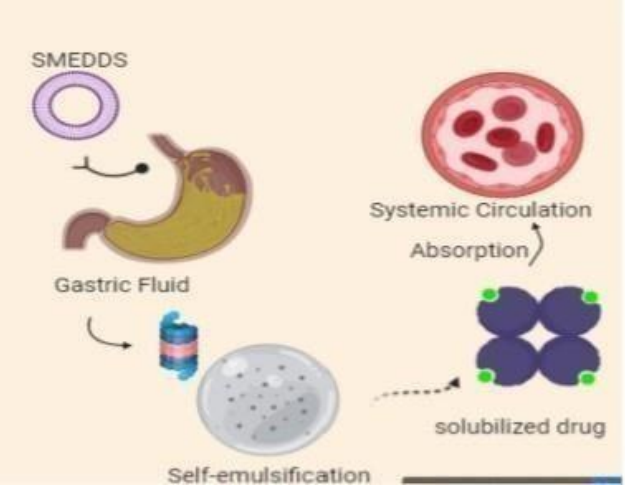

Fig. No 13 Self – Emulsifying

K. Liquisolid Methods:

When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted 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 the desirableflow characteristics. Liquisolid solid system is acceptably flowing and compressible powdered forms of liquid medications. In the concept of liquisolid system, liquid drugs having low aqueous solubility dissolved in suitable non-volatile solvents, converted in to free flowing and radially compressible powder by simple admixture with selected powdered excipients referred as carrier and coating materials. Microcrystalline and amorphous cellulose and silica powders may be used as coating materials [38,39].

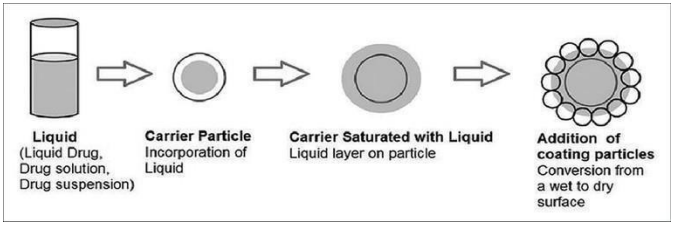

Fig. No 14 Liquisolid Methods

L. Salt-formation:

It is well documented that the influence of the changes in pH inside the gastrointestinal tract upon the bioavailability of pharmaceuticals. The absorption of drug is largely dependent upon diffusion, which vary with pH of the individual regions within the gastrointestinal tract, the pKa of the drug and permeability which are not only moderated by the surface area of the region in which it is released, but also the regional pH effects upon drug ionization. By applying a pH change, poorly water-soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water. While the significance of critical parameters like salt selection and pH adjustment has been stressed on pre- formulation, the use of pH altering excipients within drug delivery systems is also of significant utility. pH adjustment can in principle be used for both oral and parenteral administration. Because blood is a strong buffer, upon intravenous administration the poorly soluble drug may be precipitate with pH between 7.2 –7.4. To assess the suitability of the approach, the buffer capacity and tolerability of the selected pH is important to consider. In the stomach the pH is around 1 to 2 and in the duodenum thepH is between 5-7.5, so upon oral administration the degree of solubility is also likely be influenced as the drug passes through the intestines. Solubilized excipients that boost environmental pH within a dosage form (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 basicdrugs.

M. Microemulsion:

A microemulsion is an optically clear, transparent, thermodynamically stable, isotropic translucent system, contain a mixture of oil, surfactant and hydrophilic solvent which dissolve a poorly aqueous soluble drug. HLB and non-toxicity are the parameters for selecting a surfactant. When the formulations come into contact with water, they self-emulsify, forming a highly clear emulsion of small, homogeneous oil droplets carrying the solubilized weakly soluble medication. Microemulsions have been used to improve the solubility of numerous medications that are nearly insoluble in water, as well as to incorporate proteins for oral, parenteral, and intravenous administration. The most suited formulation is an oil-in-water (o/w) microemulsion, which is intended to enhance solubility by dissolving molecules with low water solubility into an oil phase solubility.

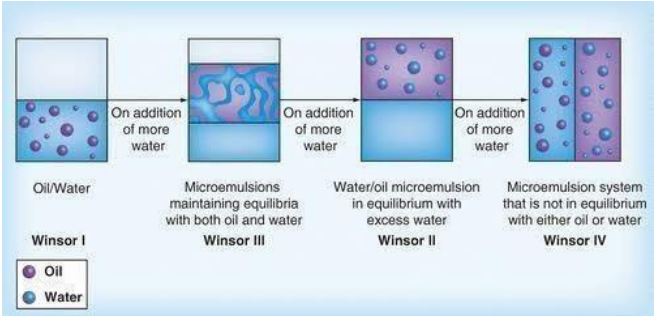

Fig. No 15 Microemulsion

N. Cryogenic Techniques:

Cryogenic techniques have been developed to enhance the dissolution rate of drugs by creating nanostructured amorphous drug particles with high degree of porosity at very low- temperature conditions. Cryogenic inventions can be defined by the type of injection device (capillary, rotary, pneumatic, and ultrasonic nozzle), location of nozzle (above or under the liquid level), and the composition of cryogenic liquid (hydrofluoroalkanes, N2, Ar, O2, and organic

solvents). After cryogenic processing, dry powder can be obtained by various drying processes like spray freeze drying, atmospheric freeze drying, vacuum freeze drying, and lyophilization [41].

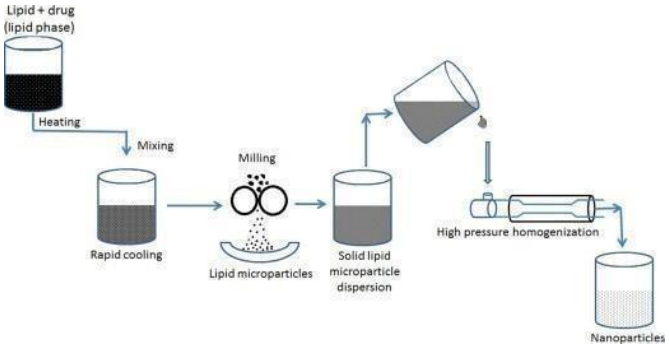

Fig. no 16 Cryogenic Techniques

O. Crystal Engineering:

The surface area of drug available for dissolution is dependent on its particle size and ability to be wetted by luminal fluids. This particle size, which is critical to drug dissolution rate, is dependent on the conditions of crystallization or on methods of comminution such as impact milling and fluid energy milling. The comminution techniques can produce particles which are highly heterogeneous, charged, and cohesive, with the potential to cause problems in downstream processing and product performance. Hence, crystal engineering techniques are developed for the controlled crystallization of drugs to produce high purity powders with well-defined particle size distribution, crystal habit, crystal form (crystalline or amorphous), surface nature, and surface energy. By manipulating the crystallization conditions (use of different solvents or change in the stirring or adding other components to crystallizing drug solution), it is possible to prepare crystals with different packing arrangement; such crystals are called polymorphs [42].

P. 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. Nanosuspension is produced by bottom-up technology and top-down technology. Top-down technology involves various methods such as nano edge, nano jet technology, milling tech

Q. Homogenization:

Homogenization is the method which is used to make a mixture of two equally non- soluble liquids the similar through. This is found by revolving one of the liquids into a state containing of very small particles circulated uniformly throughout the other liquid [43,44].

R. Micellar Solubilization:

The use of surfactants to improve the dissolution performance of poorly soluble drug products is probably the basic, primary, and the oldest method. Surfactants reduce surface tension and improve the dissolution of lipophilic drugs in aqueous medium. They are also used to stabilize drug suspensions. When the concentration of surfactants exceeds their critical micelle concentration (CMC, which is in the range of 0.05–0.10% for most surfactants), micelle formation occurs which entrap the drugs within the micelles. This is known as micellization and generally results in enhanced solubility of poorly soluble drugs. Surfactant also improves wetting of solids and increases the rate of disintegration of solid into finer particles. Commonly used nonionic surfactants include polysorbates, polyoxyethylated castor oil, polyoxyethylated glycerides, lauroyl macro glycerides, and mono- and di-fatty acid esters of low molecular weight polyethylene glycols. Surfactants are also often used to stabilize microemulsions and suspensions into which drugs are dissolved [45,46].

10. Conclusion:

Dissolution of drug is the rate determining step for oral absorption of the poorly water-soluble drugs and solubility is the basic requirement for the absorption of the drug from GIT. The various techniques described above alone or in combination can be used to enhance the solubility of the drugs. Proper selection of solubility enhancement method is the key to ensure the goals of a good formulation like good oral bioavailability, reduce frequency of dosing and better patient compliance combined with a low cost of production. Selection of method for solubility enhancement depends upon drug characteristics like solubility, chemical nature, melting point, absorption site, physical nature, pharmacokinetic behavior and so forth, dosage form requirement like tablet or capsule formulation, strength, immediate, or modified release and so forth, and regulatory requirements like maximum daily dose of any excipients and/or drug, approved excipients, analytical accuracy and so forth.

References:

[1] K. T. Saujani, A. K. Gajjar, and J. K. Saujani, ―Drug solubility: importance and enhancement techniques, ‖ ISRN pharmaceutics, vol. 2012. 2012.

[2] V. R. Vemula, V. Lagishetty, and S. Lingala, –Solubility enhancement techniques, ‖ International journal of pharmaceutical sciences review and research, vol. 5, no. 1, pp. 41-51. 2010.

[3] A. Kumar, S. K. Sahoo, K. Padhee, P. Kochar, A. Sathapathy, and N. Pathak, ―Review on solubility Enhancement techniques for hydrophobic drugs, ‖ Pharmacie Globale, vol. 3, no. 3, pp. 001-007. 2011.

[4]S. Kshirsagar, M. Choudhari, R. Sathyan, and S. Dhore, –Solubility Enhancement by Various Techniques Based on Pharmaceutical and Medicinal Chemistry Approach: An Overview,‖ Asian Journal of Pharmacy And Technology, vol. 9, no. 2, pp. 141-146. 2019.

[5]A. Paudel, Z. A. Worku, J. Meeus, S. Guns, and G. Van den Mooter, –Manufacturing of solid dispersions of Poorly water soluble drugs by spray drying: formulation and process considerations,‖ International journal of Pharmaceutics, vol. 453, no. 1, pp. 253-284. 2013.

[6]S. Jain, N. Patel, and S. Lin, –Solubility and dissolution enhancement strategies: current understanding and Recent trends,‖ Drug development and industrial pharmacy, vol. 41, no. 6, pp. 875-887. 2015.

[7]M. A. Sajid, and V. Choudhary, –Solubility enhancement methods with importance of hydrotropy,‖ Journal Of Drug Delivery & Therapeutics, vol. 2, no. 6, pp. 96-101. 2012.

[8]D. Sharma, –Solubility enhancement strategies for poorly water-soluble drugs in solid dispersions: A Review,‖ Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm, vol. 1, no. 1. 2016.

[9]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, vol. 3, No. 4, pp. 942-956. 2012.

[10]M. Patel, A. Tekade, S. Gattani, and S. Surana, –Solubility enhancement of lovastatin by modified locust Bean gum using solid dispersion techniques,‖ AAPS PharmSciTech, vol. 9, no. 4, pp. 1262-1269. 2008.

[11]B. Bonthagarala, V. Dasari, and V. Kotra, –Solubility enhancement effect at absorption site on Bioavailability of ritonavir using liquisolid technique,‖ Therapeutic delivery, vol. 10, no. 5, pp. 295-310. 2019.

[12]Y. S. Thorat, I. D. Gonjari, and A. H. Hosmani, –Solubility enhancement techniques: a review on Conventional and novel approaches,‖ International journal of pharmaceutical sciences and research, vol. 2, No. 10, pp. 2501. 2011.

[13]Y. Kato, E. Hayakawa, K. Furuya, and A. Kondo, –Method for solubilization of interferon,‖ Google Patents, 1987.

[14]K.-N. Kim, J.-H. Son, and H.-S. Kim, –Solution solubilization composition of insoluble material and method For solubilizing insoluble material using same,‖ Google Patents, 2019.

[15]M. Yazdanian, K. Briggs, C. Jankovsky, and A. Hawi, –The –high solubility‖ definition of the current FDA guidance on biopharmaceutical classification system may be too strict for acidic drugs,‖ Pharmaceutical research, vol. 21, no. 2, pp. 293-299. 2004.

[16]Y. Yang, D. Teng, J. Zhang, Z. Tian, S. Wang, and J. Wang, –Characterization of recombinant plectasin: solubility, antimicrobial activity and factors that affect its activity,‖ Process biochemistry, vol. 46, no. 5, pp. 1050-1055. 2011.

[17]Savjani KT, Gajjar AK, Savjani JS. Drug Solubility: Importance and Enhancement Techniques. ISRN Pharmaceutics Article ID195727, 2012, 1-10, Doi:10.5402/2012/195727.

[18]N. Blagden, M. de Matas, P.T. Gavan, P. York. Crystal Engineering of active pharmaceutical ingredients to Improve solubility and dissolution rates, Advanced Drug Delivery Reviews, 2007; 59(7):617-630.

[19]M. Vogt, K. Kunath, J.B. Dressman. Dissolution Enhancement of fenofibrate by micronization, cogrindingAnd spray-drying: comparison with commercial Preparations, European Journal of Pharmaceutics and Biopharmaceutics. 2008; 68(2):283-288.

[20] Chaumeil JC. Micronization: a method of improving the Bioavailability of poorly soluble drugs, Methods and Findings in Experimental and Clinical Pharmacology. 1998; 20(3):211-215.

[21] Z, Maurya N, Mishra KS, Khan I. Solubility Enhancement of Poorly Water Soluble Drugs: A Review. International Journal of Pharmacy & Technology. 2011; 3(1):807-823.

Riehemann K, Fuchs H, Schneider SW, Luger TA,Godin B, Farrari M. Nanomedicine- Challenge andPerspectives. Chem. Int. Ed. Engl. 2009; 48:872-897. [23]Md. MofizurRahman, Abul Bashar Ripon Khalipha,Jamal Ahmed, Md. AbShuaibRafshanjani, ShanjidaHaque,Methods of Solubility and Dissolution Enhancement forPoorly Water Soluble Drugs: A Review. 2014; 3(5):107-130

[24]Sareen S, Mathew G, Joseph L. Improvement In Solubility of Poor Water-Soluble Drugs By Solid Dispersion, International Journal of Pharmaceutical Investigation: Review Article. 2012; 2(1):12-17.
[25]Mohanachandran PS, Sindhumol PG, Kiran TS. Enhancement of Solubility and Dissolution Rate: An Overview, Pharmacie Globale International Journal of Compehensive Pharmacy. 2010; 1(4):1-10.
[26] Wong DH, Kim MS, Lee S, Jeong SP, Hwang SJ. Improved physicochemical characteristics of felodipineSolid dispersion particles by supercritical anti-solvent Precipitation process, International Journal of Pharmaceutics. 2005; 301:199-208.
[27] Dohrn R, Bertakis E, Behrend O, Voutsas E, Tassios D. Melting point depression by using supercritical CO2 for a Novel melt dispersion micronization process, Journal of Molecular Liquids. 2007, 131-132.
[28] Sekiguchi K, Obi N. Studies on absorption of eutectic Mixtures. I.A. comparison of the behaviour of eutectic Mixtures of sulphathiazole and that of ordinary Sulphathiazole in man, Chemical and Pharmaceutical Bulletin. 1961; 9:866-872.
[29] Kumar P, Singh C. A Study on Solubility Enhancement Methods for Poorly Water Soluble Drugs, American Journal of Pharmacological Sciences. 2013; 1(4):67-73.
[30] Habib MJ. Pharmaceutical solid dispersion Technology, Technomic Publishing Company, Inc. Lancaster, Pennsylvania (U.S.A.), 2001, 1-36.
[31] Higuchi T, Ikeda M. Rapidly dissolving forms of digoxin: Hydroquinone complex, J Pharm Sci. 1974; 63(5):809-811.
[32] Vasconcelos T, Sarmento B, Costa P. Solid dispersions as Strategy to improve oral bioavailability of poor water Soluble drugs, Drug Discov. Today, 2012; 12(23-24):1068-1075.
[33] Rogers TL, Hu JH, Yu ZS, Johnston KP, Williams RO, III A novel particle engineering technology: spray-freezing Into liquid. Int J Pharm. 2002; 242:93-100.
[34] Rogers TL, Nelsen AC, Hu JH, Brown JN, Sarkari M, Young TJ et al. A novel particle engineering technology To enhance dissolution of poorly water soluble drugs: Spray-freezing into liquid, Eur J Pharm Biopharm. 2002; 54:271-280.
[35] Hu JH, Rogers TL, Brown J, Young T, Johnston KP, Williams RO. Improvement of dissolution rates of poorly Water soluble APIs using novel spray freezing into liquid Technology. Pharm Res. 2002; 19:1278-1284.
[36] Akhilesh D, Mehta H, Prabhakara P, Kamath JV. Enhancement of Solubility by Complexation with Cyclodextrin and Nanocrystallisation, InternationalResearch Journal of Pharmacy. 2012; 3(5):100-105.
[37] Devil NKD, Rani AP, Javed M, Kumar KS, Kaushik J, Sowjanya. Cyclodextrins in pharmacy-An overview, Pharmacophore, 2010; 1(3):155-165.
[38] Patel M, Shah A, Dr. Patel NM, Dr. Patel MR, Patel Dr.KR. Nanosuspension: A Novel Approach for Drug Delivery System, Journal of Pharmaceutical Science and Bioscintic Res. 2011; 1(1):1-10.
[39] Nagabandi VK, Tadikonda R, Jayaveera KN. Enhancement of dissolution rate and micromeritics of Poorly soluble drug ketopr ofen by liquisolid technique, Journal of Pharmaceutical and Biomedical Sciences. 2011; 9(9):1-6.
[40]Khalid ME, Ahmed M. Samy, Mohamed I. Fetouh for Mulation and evaluation of Rofecoxib Liquisolid Tablets, International Journal of Pharmaceutical Sciences Review And Research. 2010; 3(1):135-142.
[41]H. Leuenberger, ―Spray freeze-drying—the process of choiceFor low water soluble drugs?‖ Journal of Nanoparticle Research,Vol. 4, no. 1-2, pp. 111–119, 2002.
[42]M. S. Suleiman and N. M. Najib, ―Isolation and physico-Chemical characterization of solid forms of glibenclamide,‖International Journal of Pharmaceutics, vol. 50, no. 2, pp. 103–109, 1989
[43]Y. S. Thorat, I. D. Gonjari, and A. H. Hosmani, ―Solubility enhancement techniques: a review on Conventional and novel approaches,‖ International journal of pharmaceutical sciences and research, vol. 2, No. 10, pp. 2501. 2011.
[44]H. Kaur, and G. Kaur, ―A critical appraisal of solubility enhancement techniques of polyphenols,‖ Journal of Pharmaceutics, vol. 2014. 2014..
[45]A. Martin, Physical Pharmacy, Willaims and Wilkins, Balti-More, Md, USA, 4th edition, 1993.
[46]C. D. Rangel-Yagui, A. Pessoa, and L. C. Tavares, ―Micellar sol-Ubilization of drugs,‖ Journal of Pharmacy and Pharmaceutical Sciences, vol. 8, no. 2, pp. 147–163, 200