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A Review of Solubility Enhancement Techniques

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ABSTRACT

The solubility of drugs is an important factor for pharmaceutical formulation. The solubility of the drug more important for the success of the drug should reach the site of action. The bioavailability and the solubility of the drug, are also important for the pharmacological effect of any formulation, especially in the case of oral dosage form .so many times to formulate poorly water-soluble drugs becomes very challenging. Absorption and dissolution rates may decrease by the poor solubility of the drug, so the solubility of the drug is important to improve by methods like salt formulation, solid dispersion, co-solvency, the addition of solubilizing agent, to enhance the dissolution rate of the drug all these approaches are mostly used, sometimes the desired bioavailability enhancement of the drug by these techniques may not be achieved always. In this review, we will study the several techniques which are used to increase the solubility of poorly soluble drugs by reducing particle size, adjustment of pH, solid dispersion and hydrotrophy, etc.

Keywords: Solubility Enhancement, bioavailability, hydrotrophy, solid dispersion.

I. INTRODUCTION

A number of methodologies can be adapted to improve Solubilization of poor water soluble drug and further to Improve its bioavailability. The techniques generally employed for solubilization of drug includes Micronization, chemical modification, pH adjustment, Solid dispersion, complexation, cosolvency, micellar Solubilization, hydrotropy etc. Solubilization of poorly Soluble drugs is a frequently encountered challenge in Screening studies of new chemical entities as well as in Formulation design and development.[1, 2] Any drug to be Absorbed must be present in the form of an aqueous Solution at the site of absorption. As Solubility & Permeability is the deciding factor for the in-vivo Absorption of the drug, these can be altered or modified By enhancement techniques like. The term 'solubility' is Defined as maximum amount of solute that can be Dissolved in a given amount of solvent. It can also be defined quantitatively as well as qualitatively. Quantitatively it is defined as the concentration of the Solute in a saturated solution at a certain temperature. In Qualitative terms, solubility may be defined as the Spontaneous interaction of two or more substances to Form a homogenous molecular dispersion. A saturated Solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug is represented through various concentration expressions such as parts, Percentage, molarity, molality, volume fraction, mole Fraction.

Solubility: - Solubility can be defined by 1 gm of solute is dissolved by the number of milliliters of solvent.

"Quantitative solubility": - It can be as defined as the milligram of solute particles that are needed to create a saturated solution.

"Qualitative solubility": -It is possible to define qualitative solubility as when the two phases are combined to form a homogeneous mixture. According to the introduction of the combinatorial chemistry, then the properties of the newly developed active compound will get shift towards the higher molecular weight and the lipophilicity of the compounds will get increased and resulting in a decrease in the aqueous solubility of the drug. [2, 3]

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Definitions of solubility:-

Definition	Parts of solvent required for one 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

Poor absorption has many potential causes: -it is possible to say any substance is poorly water-soluble when:-

1. <100µg/ml aqueous solubility.
2. Bad dissolution: <0.1 mg/cm2/min, intrinsic dissolution rate.

"Biopharmaceutics classification system (BCS)": Amidon et al.first developed BCS in1995 The US Food and Drug Administration (FDA) introduced it and following its permeability and solubility the drugs are classified into four groups. As the rate-limiting step for the absorption of the drug due to low solubility, solubility problems are mostly faced in class 2 and class 4 of the system facing dissolution. [4, 5]

"Class"	**"Permeability"**	**"Solubility"**
1.	"High"	"High"
2.	"High"	"Low"
3.	"Low"	"High"
4.	"Low"	"Low"

Process of solubilization:- Solubilization is a process that requires the breaking of intermolecular or intrinsic solute's bond. Separation of the solvent molecules to provide space for the solute in the solvent, the interaction between the molecule and ion of the solute and the solvent.

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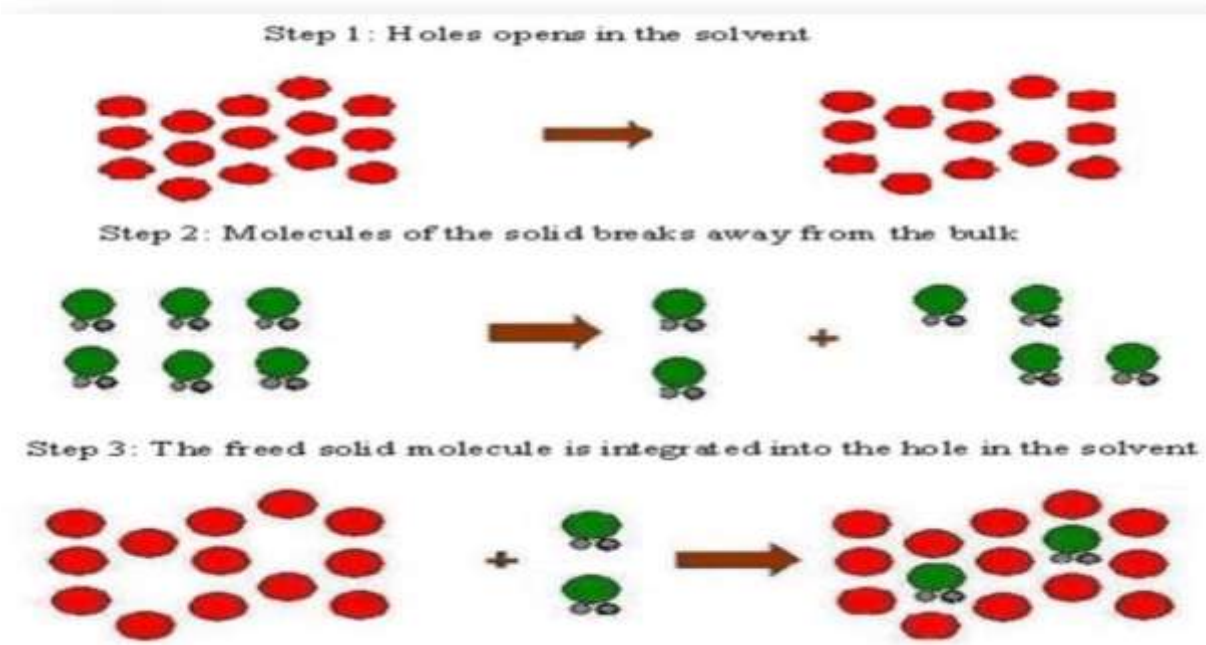

Fig 1:- process of Solubilization

Solubility affecting factors:-

1. "Nature of solute and solvent": the essence of the solvent and of the solute depends on the composition of the solute in a quantity that is unique to the solvent at a specific temperature e.g.:- only 1gm of lead in 100gm of water at room temperature, and the second one that chloride can be dissolved while 200 grams of zinc chloride can be dissolved.

2."Size of particles": solubility can be influenced by the size of the particle. When the size of the particle gets decreases then the surface area to volume ratio also gets increases. And when the surface area of the particle gets increases then results in more interaction with the solvent.

3. **Molecular size: -** solubility also can be influenced by the molecular size of the particle. The substance's solubility gets decreased when molecules have a higher molecular weight and higher molecular size.

4. **"Temperature":** it can also affect the solubility of the drugs. If the solution process is absorbing the energy then the solubility will go to increase with an increase in temperature. If the solution process releases the energy then the solubility will go to decrease with an increase in temperature.

5 "Pressure": For the liquids and solid solutes, the solubility is not affected by a change in pressure but for the gaseous solutes, solubility increases as the pressure increases and decreases as the pressure decreases. [8, 9]

"Importance of Solubility"

Most common or convenient route of drug delivery is oral ingestion because of its cost effectiveness, ease of administration, minimal sterility constraints, high compliance with patients, and versatility in the dosage design. [10]

In other dosage forms also solubility plays an important role, the other dosage forms are like parenteral formulations as well. One of the most relevant parameters is solubility that comes to attaining the optimal blood circulation for attaining the desired therapeutic responses or actions. Water-insoluble drugs also need optimum doses after oral administration to achieve therapeutic plasma concentration. A mostly drug that tends to be absorbed must be present at the absorption site in the form of an aqueous solution. The main solvent choice is water for the formulations of liquid pharmaceuticals. [11]

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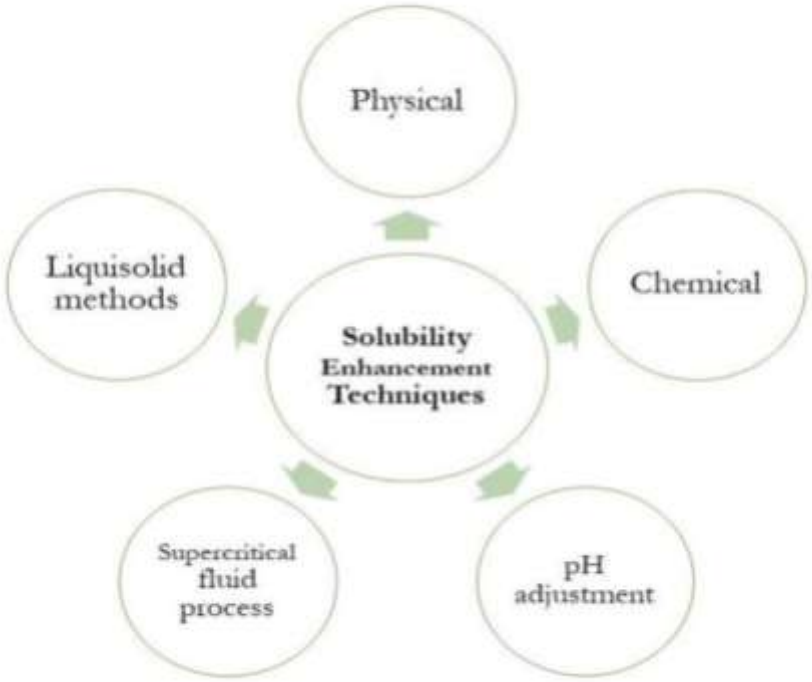

Fig: 2 Broad classification of solubility enhancement technique

1. Physical Modification
(a)Particle size reduction
•Micronization
•Nanosuspension **(b)Modification of crystal habit**

- Polymorphs
- Pseudopolymorphs

(c) Drug dispersion in carriers

- Solid solutions
- Solid dispersion

(d) Solubilization by surfactants

- Microemulsion
- Self-micro emulsifying drug delivery system

(e) complexation
2.Chemical modification
(a) Hydrotrophy

- Co-solvency
- Salt formation

3. PH adjustment
4. Supercritical fluid process
5. Liquisolid methods

1.Physical modification
(a) Particle size reduction

Solubility of drug is also related to particle size of drug. By reducing particle size, surface Area increases which improves the dissolution property of drug. Drug particle size is often related to bioavailability of poorly soluble drugs. Particle size reduction is done by milling Techniques using colloid mill, jet mill etc. The saturation solubility of drug does not change; This is not suitable for drugs having a high dose number.

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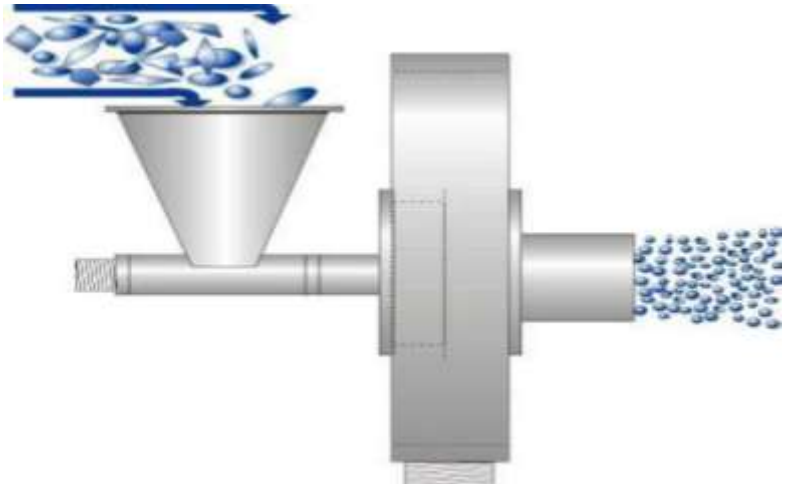


Fig:-3 Particle size reduction

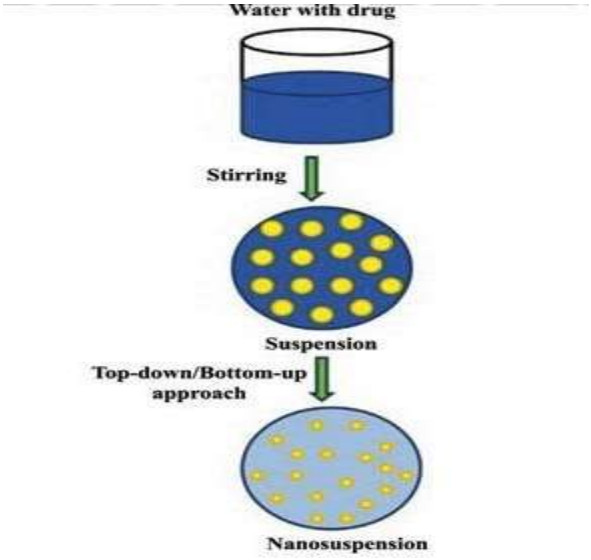
ADVANTAGES:-

- Liquid forms can be rapidly developed for early Stage testing (pre-clinical) that can be converted into solids for later clinical development.
- Typically, low excipients to drug ratios are required.
- Formulations are generally well tolerated Provided that strong surfactants are not required for stabilization. Generally, crystal forms are chemically and physically more stable than amorphous particles.
- A method to consider for stubborn compounds that defeat previous attempts to increase Solubility.

DISADVANTAGES:-

- Due to the high surface charge on discrete small Particles, there is a strong tendency for particle Agglomeration.
- Developing a solid dosage form with a high pay Load without encouraging agglomeration may be technically challenging.
- Technically, development of sterile intravenous Formulations is even more challenging.

Nanosuspension:-



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This technology is used to poorly soluble drugs that are insoluble in Water & oils.

Nanosuspension is biphasic system which consists of nano size particle in aqueous vehicle. For Parenteral and pulmonary administration or oral and tropical use Nano size drug particles are stabilized by surfactant. In nano suspension, particle size Distribution of solid particle is usually less than one micron. And average particle size Range is 200 and 600nm. This process applied to tarazepide, atovaquone, amphotericin & paclitaxel and buparvaquone. Various methods for nanosuspension preparation include Nanocrystals, DissoCubes, Nanopore and Nano edge. [9]

ADVANTAGES:-

- Size of drug particles is reduced which increase the surface area, which in turn increase Dissolution, solubility & bioavailability.
- Nanosuspension increase drug permeability.
- Nanosuspension increase duration of action of residence.
- Nanosuspension increase bio adhesion of drug
- It exerts advantage of high drug loading.
- Avoidance of organic solvent.

DISADVANTAGES:-

• The main problem suffer in nanosuspension is instability due to crystal growth, Agglomeration, Ostwald ripening.

(b) MODIFICATION OF CRYSTAL HABBIT:-

- **Polymorphs:-**The ability of a substance to crystallize in more Than one crystalline form is polymorphism. Polymorph is an agent having ability to crystallize in more than one crystalline form. It is Possible that solid can crystallize in different forms or Polymorphs. Polymorphs can vary in melting point. Since the Melting point of the solid is related to solubility, so polymorphs will have different solubility. [4]
- **Pseudo polymorphs:-**Polymorphism is the ability of solid material to exist in 2 or more different crystalline Forms with different arrangements in crystal lattice. Polymorphs are different crystalline Forms. Crystalline forms of drugs are chemically same but they have different

Physiochemical properties like melting point, texture, density, solubility, stability. Similarly, amorphous form of drug is more suitable than crystalline form. Due to more Surface area and high associated energy.

Order of different solid form of drugs.

Amorphous > Metastable polymorphs > Stable polymorphs.

(C) DRUG DISPERSION IN CARRIER:-

Solid solutions:-In this two crystalline solid are blend that exist as a new crystalline solid. In homogenous one phase system, two components are crystallized together to form a Mixed crystal. As compare to simple enteric system it yields much higher rate of Dissolution.[12]

Solid dispersion:- The concept of solid dispersion was proposed by Sekiguchi & Obi. Solid dispersion is a useful pharmaceutical technique for enhance the rate of dissolution, absorption & therapeutic efficacy of drugs. Solid dispersion term refers to a group of solid products generally consists a hydrophilic matrix & a hydrophobic drug. Commonly used hydrophilic carriers are polyethylene glycols, polyvinyl pyrrolidone, and plasdone-S630. In the formation of solid dispersion surfactants are many times used.

Example:-Myrj-52, Tween-80, Sodium lauryl sulphate, Pluronic-F68 and Docusate sodium. This process was applied to halofantrine, celecoxib, ritonavir to increase the solubility. Techniques to prepare solid dispersion of hydrophobic drugs to enhance their aqueous Solubility are following:

- Fusion process: In this process, carrier is heated above its melting point temperature and drug is incorporated into matrix with constant stirring mixture is cooled to disperse the drug throughout the matrix.
- Solvent evaporation method: In a suitable organic solvent, carrier and active ingredient are dissolved. Solvent is evaporated at an elevated temperature under vacuum conditions to produce a solid residue.
- Commonly used solvents are chloroform, ethanol, or a mixture of dichloromethane and ethanol.

ADVANTAGES:-

- The thermal decomposition of drugs and carrier can be prevented.

DISADVANTAGES:-

- Expensive
- Difficult to remove complete liquid solvent
- Difficult to find out common solvent

Hot-melt extrusion: In polymer industry this method is commonly used. In hot solvent

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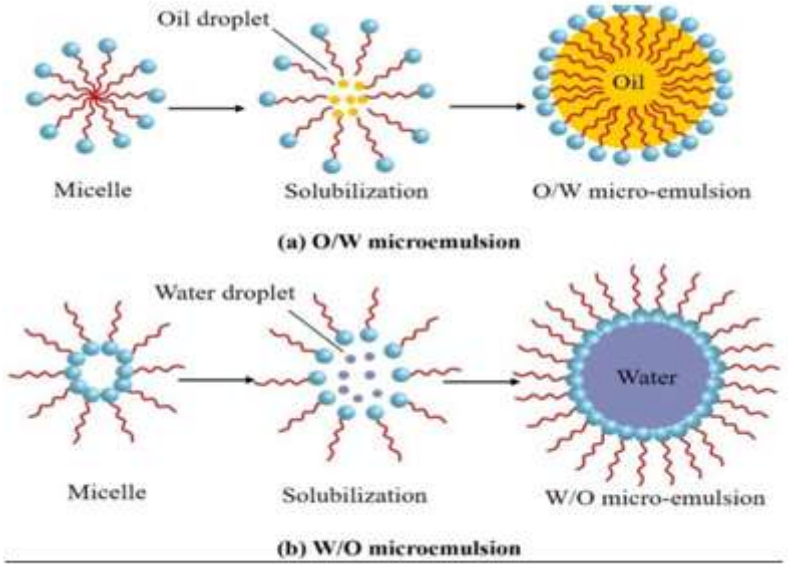
Extrusion method, the mixing of components is induced by extruder. Like fusion process, Drug and carrier are immiscible. The drug/carrier combination is only exposed to an Elevated temperature for about one minute with the hot melt extrusion method, which Allows for the processing of drugs that are slightly thermo labile. [2,9]

(d). Solubilization by surfactants:-

•**Microemulsion**:

A microemulsion is an optically clear, transparent, thermodynamically Stable, isotropic translucent system, contain mixture of oil, surfactant and hydrophilic solvent which dissolve a poorly aqueous soluble drug. HLB and non-toxicity are the 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.



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ADVANTAGES:-

Drug release from well-developed microemulsion pre-concentrates is usually not dependent on digestion. As a result, without the need for meal co-administration, optimum bioavailability and repeatability can be expected.

DISADVANTAGES:-

- Validation becomes more difficult for formulations with several components.
- Self-emulsifying drug delivery system: The mixture of oil, surfactant, co surfactant, and one or more hydrophilic solvents in the absence of an external phase (water) and the cosolvent produce a clear isotropic solution. The self-emulsifying solution is a type of solution that has the ability to emulsify itself. Some researchers have also called it "micro emulsion pre-concentrate." When taken orally, these new colloidal compositions behave like oil-in-water microemulsions.

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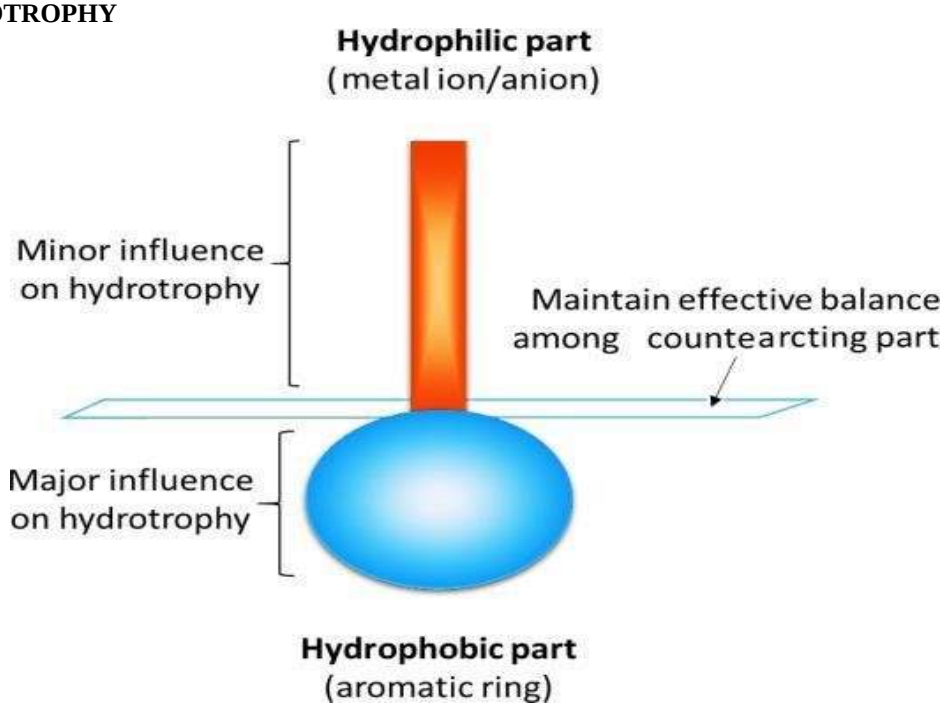
(e).COMPLEXATION:-

Drugs have been complexed with cyclodextrins to improve water solubility and drug Stability. In pharmaceutical formulations, the most often used β-cyclodextrin derivatives with improved water solubility are utilised. Because cyclodextrins are big molecules with Molecular weights larger than 1000 Da, they are unlikely to penetrate the skin easily. Skin Penetration has been reported to increase and decrease as a result of cyclodextrin Complexation. CDs can also be utilised as membrane permeability enhancers and stabilising Agents in addition to their solubility enhancement application. The presence of cyclodextrins Improves permeability through biological membranes. In pulmonary drug delivery systems, CDs can also be used as a permeability enhancer.

1.CHEMICAL MODIFICATIONS:-

(a)HYDROTROPHY



Hydrotrophy is a solubilization process in which a high amount of a second solute is added to Increase the aqueous solubility of a third solute. The method by which it improves solubility is more directly associated with complexation, which involves a weak contact between hydrotropic agents such as sodium alginate, sodium acetate, sodium benzoate, urea and poorly soluble drugs. The "salting in" of non-electrolytes known as "hydrotropic salts" is caused by many salts with large anions or cations that are themselves extremely soluble in Water, a process known as "hydrotropism." Hydrotropic solutions are non-colloid and have a Weak contact between the hydrotropic agent and the solute.

ADVANTAGES:-

- Hydro trophy has a high selectivity and doesn't require emulsification, and its solvent Nature is independent of pH.
- It does not need the use of organic solvents, or the preparation of an emulsion system.

DISADVANTAGES:-

- Gather alone in solution
- Eg:-ketoprofen, aceclofenac, salicylic acid, cefixime, tinidazole, frosemide, Amoxicillin.

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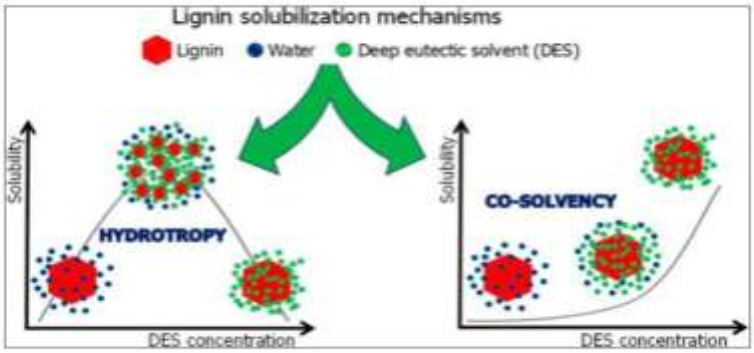
(C) co-solvency:-



Co-solvency is a mixture of one or more miscible liquids used to improve the solubility of Drugs. The addition of a co-solvent solution can improve the solution's solubility and Miscibility, as well as its dissolution. In comparison to the simple drugs, the co-solvent Enhanced the low solubility drug by almost a thousand times. A co-solvent technique may Be appropriate for poorly soluble lipophilic or highly crystalline molecules with a highSolubility in the solvent mixture. Because of the low toxicity of many co-solvents and their Relative ability to solubilize nonpolar pharmaceuticals, it has primarily been used in parenteral dosage forms. To lower the solvent content before administration, parenteral Formulations may require the addition of water or a dilution step using an aqueous media. To improve the solubility of weakly soluble substances, co-solvents can be coupled with various Solubilization procedures and pH adjustments. The use of cosolvents to improve the Solubility of poorly soluble pharmaceuticals is a very useful strategy. Propylene glycol, Ethanol, glycerin, and polyethylene glycol are the most common low-toxicity cosolvents used in parenteral administration. Because of their considerable solubilization capacity for poorly soluble drugs and their comparatively low toxicity, dimethyl sulfoxide (DMSO) and Dimethylacetoamide (DMA) have been widely employed as cosolvents.

ADVANTAGES:-

- Simple and rapid to formulate, produce and evaluate.
- It can be combined with other solubilization techniques and pH adjustment to further increase solubility of poorly soluble Compounds

DISADVANTAGES:-

- As with all excipients, the toxicity and tolerability Related with the level of solvent administered has to be considered.
- Uncontrolled precipitation occurs upon dilution with aqueous media. The precipitates may be Amorphous or crystalline and can vary in size.
- Many of the insoluble compounds Phares works with are unsuited to co-solvents alone, particularly for intravenous administration.
- This is because the drugs are extremely insoluble in Water and do not readily redissolve after Precipitation from the co-solvent mixture.
- In These situations, there is a potential risk for Embolism and local adverse effects at the Injection site.
- As with all solubilized forms, the chemical Stability of the insoluble drug is worse than in a crystalline state.

Co-solvent products: Nimodipine Intravenous Injection (Nimotop®, Bayer) and Digoxin Elixir Pediatric (Lanoxin®, GSK) are examples of co-solvent formulations.

(d) Salt Formation:

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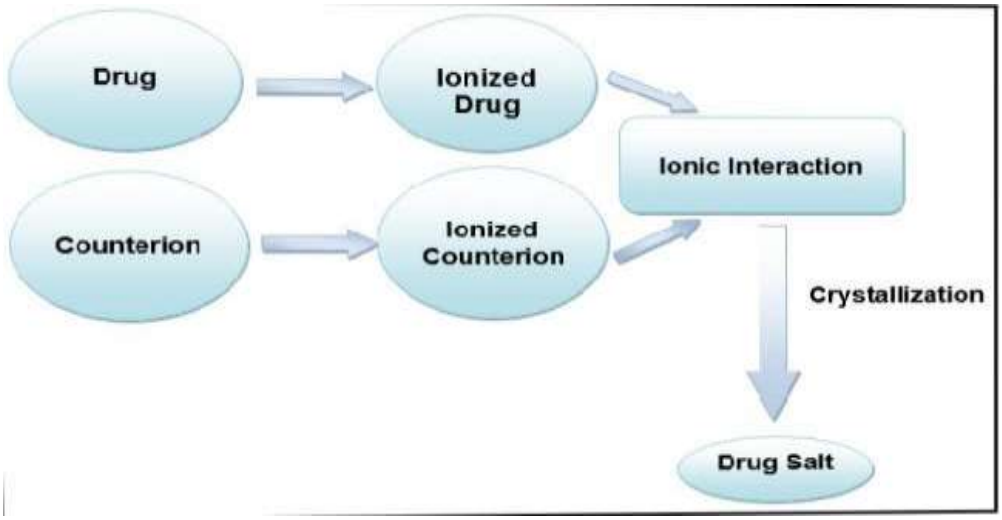

Salt formation techniques are is used to improvement of the solubility and dissolution of drug. This method is for the purpose to see any reaction of different drug or chemical reaction. Salt forms when the drug is ionized formed. It's having different method like physiochemical property and affects characteristics stability, bioavailability, Purification and manufacturability of the drug. Salt formation of low soluble drug candidates has been an approach for numerous periods to enhance solubility.
Ex. Aspirin, Theophylline, Barbiturates etc

3. PH ADJUSTMENT:-

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 pre-clinically 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.

ADVANTAGES:-

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

DISADVANTAGES:-

- Risk for precipitation upon dilution with aqueous media having a pH at which the compound is less soluble. Intravenously this may lead to emboli, orally it may cause

Variability. Tolerability and toxicity both local and systemic related with the use of a non physiological pH and extreme pH should be considered.

- As with all solubilized and dissolved systems, a dissolved Drug in an aqueous environment is frequently less stable chemically compared to formulations crystalline solid. The selected pH may accelerate hydrolysis or catalyze other Degradation mechanisms.

6. SUPER CRITICAL FLUID PROCESS:-

Supercritical fluids (SCFs) can dissolve nonvolatile solvents, with the critical point of carbon dioxide. It is safe, environmentally Friendly, and economical. A SCF exists as a single phase above its Critical temperature and pressure. SCFs have properties useful to product processing because they are intermediate between those of pure liquid and gas. Moreover, the density, transport properties (such as viscosity and diffusivity), and other physical properties (such as dielectric constant and polarity) vary considerably with Small changes in operating temperature, pressure or both around the critical points. Unique processing capabilities of SCFs, long recognized and applied in the food industry have recently been adapted to pharmaceutical applications. Commonly used Supercritical solvents are carbon dioxide, nitrous oxide, ethylene, Propylene, propane, n-

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pentane, ethanol, ammonia, and water. Several methods of SCF processing have been developed to Address individual aspects of these shortcomings, such as Precipitation with compressed antisolvents process (PCA), Rapid Expansion of Supercritical Solutions, Gas Antisolvent Recrystallization, Precipitation with Impregnation or infusion of Polymers with bioactive materials, Compressed Fluid Antisolvent, Solution enhanced Dispersion by Supercritical Fluid, solution enhanced dispersion by SCF (SEDS), aerosol supercritical Extraction system (ASES) and supercritical antisolvents processes(SAS).

ADVANTAGES:-

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

7.LIQUID SOLID METHODS:-

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

ADVANTAGES:-

- Provides acceptably flowing and compressible powdered Forms of liquid medications.Method improves the solubility, bioavailability of orally Administered water insoluble and is applicable in industry.
- Useful for the formulation of oily drugs/liquid drugs.
- Drug release can be modified by using different carrier and Additives like PVP,

PEG 60000, Hydroxy Propyl Methyl cellulose and Eudragit etc.

- A number of poorly soluble drugs can be formulated in to the system.
- This system is specifically for the powdered liquid Medications.
- Production cost is low compared to that of preparation of Soft gelatin capsules.

DISADVANTAGES:-

•It requires recipients of high adsorption properties and high specific surface area.

•It is not applicable to high dose insoluble drugs (>100 mg)

II. CONCLUSION:-

Dissolution of drug is the rate determining step for Oral absorption of the poorly water soluble drugs, which can subsequently affect the in vivo Absorption of drug. Because of solubility problem Of many drugs the bioavailability of them gets Affected and hence solubility enhancement becomes necessary. The basic approaches Followed by all the currently available technologies engaged in the solubility and Dissolution enhancement is to maximize the Bioavailability and therapeutic efficacy. To Overcome the solubility problem various solubility Enhancement methods are develop today which is industrial applicable. By using newer techniques which are discussed above it is possible to improve solubility of poorly water soluble drugs.

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