Solubility Enhancement Techniques: A Comparative Study

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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. BCS 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 is

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

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 procedure to 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]. 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].

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 [1]. 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 [6]. 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 its 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 rises with 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:

1. Physical modification
2. Chemical modification
3. And other techniques [10]

PHYSICAL INVESTIGATIONAL CHANGES:

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 lead 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].

SOLUBILITY EXPRESSION:

Table 1: Solubility classification

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]

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]

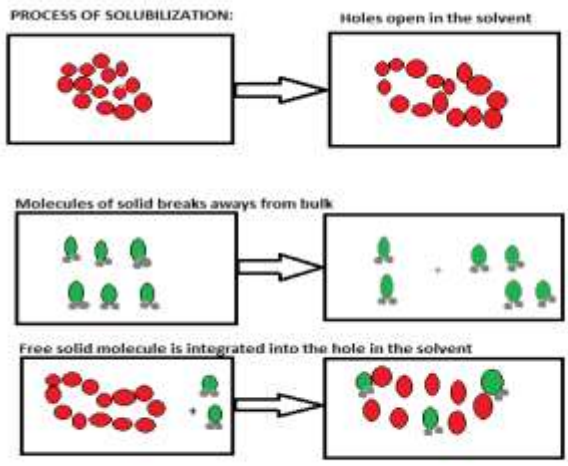

Fig.1: Solubilization process

Bio-Pharmaceutics classification system (BCS):

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

Table 2: BCS with examples

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

The factor affect solubility is given:

- Particle size: Size of the solid particle affects solubility since for example element becomes smaller; surface areas volume ratio raise of surface area, which allows to leads greater communication/interact through the solvent.
- Temperature: Rising in temperature of solubility material enhancement is normally probable.
- Nature of solute and solvent: The drug solubility is owing to polarity of the solvent which is dipole movement and the adding of H-bonding between the solute and solvent is needed [7].
- Pressure: The solid and liquids solubility not affected water in higher pressure. Solubility of gases knowingly rises by pressure. When the increase in solubility is directly proportional to the increase in pressure.
- Polymorphs: Volume for material to crystallize in which there is more than one crystalline form is polymorphism. Polymorphs can also differ in the melting point.

- PH: Maximum of drugs is weak electrolytes and the weak bases and weak acids undertake ionization in the solution. The drugs which have more soluble in water when they are in ionised form. Poorly water soluble drug is Unionised drug [1, 16].

TRADITIONAL SOLUBILITY ENCHANCEMENT TECHNIQUES:

The solubility enhancement technique is listed below:

1. Surfactant
2. PH adjustment
3. Co-solvency
4. Co-crystallization
5. Solubilizing agents
6. Formation of salt
7. Polymeric alteration
8. Size reduction of particle
9. Co-grinding and Co-micronization
10. Micro emulsion
11. Solvent evaporation
12. Sonocrystalization
13. Inclusion Complexation [17, 18]

ADVANCE TECHNIQUES FOR SOLUBILITY ENHANCEMENT:

The advance techniques are given below

1 Micronization
2 Homogenization
3 Nano suspension
4 Super critical fluid process
5 Spray drying
6 Hydro-trophy [1, 19]

LIMITATION:

Table 3: Advantages and limitations of solubility enhancement techniques

Method	Advantages	Limitation
Formation of salt	Best method to increase the solubility and dissolution rate of acidic nature substance and all basic drugs.	It is the high reaction with atmospheric Co2 and water which is resultant in the precipitation in low water soluble drug and displays in the epigastric stress due to alkalinity [6].
Solvent evaporation	Simple techniques and for the encapsulation of hydrophilic and hydrophobic drug	Solvent evaporation it may cause the more preparation rate [3].
Spray drying	It is technologize system for the mass production method.	Spray drying is method experimental use to mechanical force commination it may degrade in certain pharmaceuticals development, and drying might cause the thermal pressure and dreadful conditions of some products use are used of the organic solvents [1].
Micronization	This method helps in rate of dissolution in drug	The high-energy, which leads to causes break in from of drug crystal lattice, ensuing in the occurrence of disorder or formless region in the final product [2]
Hot melting extrusion	It is continuous process and not essential of any organic solvents or water.	Hot-melt extrusion is the tools have been imperfect because of temperature complex nature of the drug
Size reduction of particles	Its helps to increase in the	Reason of the more surface control on distinct lesser elements, there is a strong trend for

	surface area where volumes ratio is perfection in the solubility.	element gathering
Micro-emulsion	Preparation is easy and this technique is thermodynamic stability which leads to increase the drug loading and penetration.	The affinity of precipitation of the drug on dilution and it lead to be advanced due to dilution influence of polar head solvent. Formulations comprising numerous components become more challenge to authorize [3].
Hydro-trophy	This process is it suggests to superior solubilizing method and the solvent is independent through the PH.	Hydrotropy exhibit effects on the surfactant combination important to micelle formation, and stage display of more than one systems with the position toward the Nano- dispersions and it conduct percolation, clouding nature of the polymer and surfactants etc.
Surfactant	To improve the drug stability	Micelle development happens which it entrap with the drugs within micelles and mostly results in the raised solubility of below par soluble drugs.
Solid dispersion	To make the better wettability and also can reduced the particle size.	Low certainty of the solid dispersion conduct due to the lack of an elementary considerate of their material properties [18].
Supercritical fluid process	Process is having the low operating condition and also they can	Precipitation by infusion or impregnation of the polymers with bioactive product, Anti-solvent, Compressed Fluid, Solution improved Dispersal by the Supercritical Fluid techniques.

	recrystallized and can reduced the particle size	
Polymeric alteration	Having high molecular weight polymers and fast polymerizations rate	Bioavailability, required important to alteration drug and the crystal forms in meta-stable has done for shelf-life under a multiplicity of storage conditions
PH Adjustment	It is easy to produce and simple to formulate and analyses	Acceptability and poisonousness both native and complete related to required of a non-physiological pH, dangerous pH should be considered [7]

Table 5: List of techniques used for different drugs

Method	**Drug name**
Solubilizing	Glipizide, Gliclazide, Glyburide, Glimepiride [20]
Particle size reduction	Griseofulvin, Etoricoxib, Progesterone, Spironolactone diosmin, and Fenofibrate [21]
Solid dispersion	Celecoxib, Halofantrine, and Ritonavir [22]
Co- solvency	Etoricoxib, lornoxicam, Progesterone [23]
Micro-emulsion	Ampelospin, Clopidogrel, Valsartan, Glipizide [3]
Micellar-solubilization	Repaglinide, Rosiglitazone, Glipizide Anti-diabetic drugs, Pioglitazone Gliclazide, Glyburide and glimepiride etc [24].
Complexation	Albendazol

Supercritical fluid process	supercritical: Norfloxacin, ofloxacin, dexamethasone, Ketoprofen, Piroxicam, and Nimesulide [25]
Sonocrystalization	Celecoxib
Hydro-trophy	Theophylline, Keratolytic drug(eg. salicylic acid, lactic acid, urea) [1, 2]

TRADITIONAL TECHNIQUES:

Surfactants:

Surfactant is the method which is used to reduce the void fraction from the liquid-solid, liquid-liquid, or liquid-gas. Surfactants is widely used for the purposed to improved solubility of drug. Surfactant is the best solubility enhancing agents and for the dissolution purposed. It promotes to enhance in wetting and penetration in dissolution for solid drug as a fluid. Example is Soap (fatty acid), propylene glycol, Sodium lauryl sulfate (SLS). The advantage is to improved the drug stability [26].

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 [9].

Co-solvency:

Co-solvency is the mixture of one or more miscible liquids which is required in improving of the drug solubility. Addition of co-solvent solution can increased the solubility and miscible of the solution and show the better dissolution. This is the easy method which can do by the simple process by combining the solvent or having the mixture of solvent which increased the low solubility drug. The example of co-solvent are ethanol, propylene glycol, PEG 300 etc. Co-solvent increased the low solubility drug more than thousand times in comparisons between the simple drugs. This is extremely used in the scheme of different types of formulations has found. Its main purpose of use in the parenteral dosage as for the irritating or any special side effects of most surfactants. The lower effect different co-solvents may have comparatively better skill of co-solvents to solubilize non-polar drugs. The used of co-solvent in low solubility drug. Advantage is simple and rapid to formulate for formulation. The example for co-solvent is Dimethyl acetoamide, Dimethyl sulfodioxide [26, 27].

1. Diagram showing: Co-solvents progress solubility in the central of insoluble phases, as confirmed by a solute soluble in organic solution but insoluble in water left container. A co-solvent soluble in both phases and which is capable to soluble the solute and is add further to form a similar solution of water, organic solution, and compound in right container [28].
2.

Co-crystallization:

Co-crystallization is a method which is most frequently used to enhance the solubility. Thus the **co**-crystals typically raise the solubility in drug, which is not possible in the case, if a different molecule. For example, Telmisartan is the II class drug which has the low solubility. The efficiency of drug therapy which is highly depends on equal to the drug in blood, thus it is directly be contingent on nature of drug solubility. Solubility and dissolution is the most important factors in pharmacological effect of the drug to show the pharmacological response [29]. A drug with having good that shows the better solubility properties will show good absorption, which in turn will lead to the better bioavailability. However, nearly 40% of the drug shows low solubility in water. In line for to low solubility, the drug is absorbed slowly through a body and levels of drug in the blood are lower than the essential levels. In pharmaceutical industry, the deficiency of the properties of biopharmaceutical drugs such as unsuccessful medication constitutes 1% of the foremost cases in market. These issues are through results of the solubility property of the drug. About 70% of applicant drugs have problems to the solubility, therefore, it is a big dare in the field of pharmaceuticals to developing drugs process and drug dosage forms to show the good profile of solubility and dissolution rate of the drug, especially for oral preparations [30, 31].

Solubilizing agent:

This is the method in which solvents are used for better solubility and dissolving of drug to the body and for the better therapeutic effects **.**The Solubilizing agents like super-disintegrates such as like cross-carmellose sodium and sodium starch glycolate which is used as solubilizing compounds in different kinds of preparation which development the solubility and dissolve of drugs. Improved gum Arabic or gum karaya, an established material was estimated as carrier for dissolution improved the low soluble of drug like nimtop. The water solubility of drug anti-malarial agent tablet of halofantrine hydrochloride was amplified by the adding of caffeine and niacinamide [2, 21].

Salt Formation:

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 ionised 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 [2, 32].

Fig.3.

Diagram showing: Represent the process formation of salt

Micro-emulsion:

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 to body. 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 [19]. 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 [6, 27].

ADVANCE TECHNOLOGY:

Micronization:

Micronization is the process for the decrease of size of particle for the better solubility of drug and it enhance dissolution rate of the drug. The size reduction of particles or materials is to raise effective surface area in which its result the reduced of solubility and dissolution rate of drug. This is the process when it is used to progress dissolution rates of drugs into the biological method, in order to better bioavailability. Micronization having the higher particle size reduced the granular particle converted into the lesser than 5 microns. In this process it helps if

the surface area is increase however it decreased in particle size and solubility is rise. It shows the narrow and uniform particle size essential for development for the uniform dosage form. The different in which is utilized for the solubility enhanced in the micronization are like micro precipitation, Control crystallization, and micronizers. The advantage of micronization is having tendency to give the uniform particle size with rise in the surface area and particle distribution [2, 24].

Nanonization:

Nanosuspension is method used for the low soluble drug for the purpose of parenteral drug. The advantages of this process are the particles sizes is less than one micron and for the parenteral low soluble drug. Nowadays the various nanonization methods have been emerged to raise the bioavailability and dissolution rate of frequent drugs that have low soluble in water. This method is used for both water and oil insoluble compounds [2]. Widely used for the purpose of pharmaceutical industry for preparation of parenteral used drug this can easily bind and shows the pharmacological action of the drug. By this techniques can obtained the particles size less than 1 micron or in the average of 200 to 600nm. The various methods which is used for this Nano jet technology and nano edge process which give the better enhancement solubility of the product Advantage of nanonization is avoid any other organic solvent and give the uniform particle size which required less than one micron [33, 34].

Supercritical fluid method:

This technology is used for the size reduction of the particles. Widely used for the nano drug in which water insoluble. Application is it can use for the nonvolatile solve at the critical point of co2. The small working circumstances create the supercritical fluid approaches is an attractive for pharmaceutical research. SCF happens as a single stage above its critical pressure and temperature. These methods are useful and mostly utilized and have the intermediate into the pure liquid and gas [6]. Mostly it's varying in the temperature and the pressure which should be maintain around the critical point. This method is used in the pharmaceutical industry for the purpose to decrease in particle and in food industry. The solvents used for supercritical fluid process is ethylene, ammonia, ethanol, propanol, co2 etc. Development of the supercritical solvents like recrystallization, gas antisolvents, Bio active material. Furthermore it is widely used for the purposed of the aerosols. Advantage of supercritical process is having the low operating condition and also they can recrystallized and can reduced the particle size less than 2 to 5000microns and can also have sub-micron change level of sixe of particles [1, 7].

HYDROTROPHY:

The Hydrotropy is a solubilization process in which other solvent is used to raise the soluble of the mixtures. Due to incidence of large amount of additive it can make the better solubility in the water. Its mechanism is solubility because it related to the Complexation which involved in the weak interaction between the hydrotropic agents though, the process being used in the works to be in non-micelle-forming materials, whichever solids or solid, inorganic or sorganic, capable of solubilizing insoluble compounds [9]. In the following method the Hydrotropy is classified in three ways like as aromatic catatonics, aromatic anionic, linear anionic. The example of different Hydrotropy agents is sodium acetate, sodium alginate etc. The advantages of this process is it suggest to superior solubilizing method and the solvent is independent through the PH also have wide range of compound have been report exhibit hydrotropic conditions [21, 35].

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 [12, 36].

CONCLUSION:

The solubility enhancement techniques which are improve the solubility of the drug through different parameter. Solubility is the concept of any Physical and Chemical including the Pharmacokinetics therapy in consideration of medicine and Biopharmaceutical. The Various 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 Micronization, Nano-suspension, and Homogenization, Salt formation, Spray Drying, Solvent Evaporation, Hot-melt Extrusion, and Conventional method for solid dispersion etc. Nowadays solubility enhancement techniques is very useful for the improved the dissolution and solubility of drug.

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