

# (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.

**Introduction:** For the enhancement of the process Solubilization of poorly water-soluble drugs and further enhance the bioavailability of the drugs, a variety of methodologies can be adapted. Micronization, chemical modification, pH change, solid dispersion, co- solvency, micellar Solubilization, complexation, hydrotrophy are the common techniques usually used for the drug Solubilization process. The Solubilization process of poorly water-soluble drugs is the most challenging obstacle in the studies of screening of new chemical entities as well as in the formulation development and design. [1]

**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]

## 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	From1000-10,000”
“Insoluble	Greater than 10,000”

POOR ABSORPTION HAS MANY POTENTIAL CAUSES: - IT IS POSSIBLE TO SAY ANY SUBSTANCE IS POORLY WATER-SOLUBLE WHEN:-

1.  $<100\mu\text{g/ml}$  aqueous solubility.
2. Bad dissolution:  $<0.1 \text{ mg/cm}^2/\text{min}$ , intrinsic dissolution rate.

**“Biopharmaceutics classification system (BCS)”**: Amidon et al. first developed BCS in 1995. 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. [4-6]

“Class”	“Permeability”	“Solubility”
<b>I.</b>	“High”	“High”
<b>II.</b>	“High”	“Low”
<b>III.</b>	“Low”	“High”
<b>IV.</b>	“Low”	“Low”

[7]

**Process of Solubilization**: - Solubilization is a process that requires the breaking of intermolecular or interionic 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. [30-32]

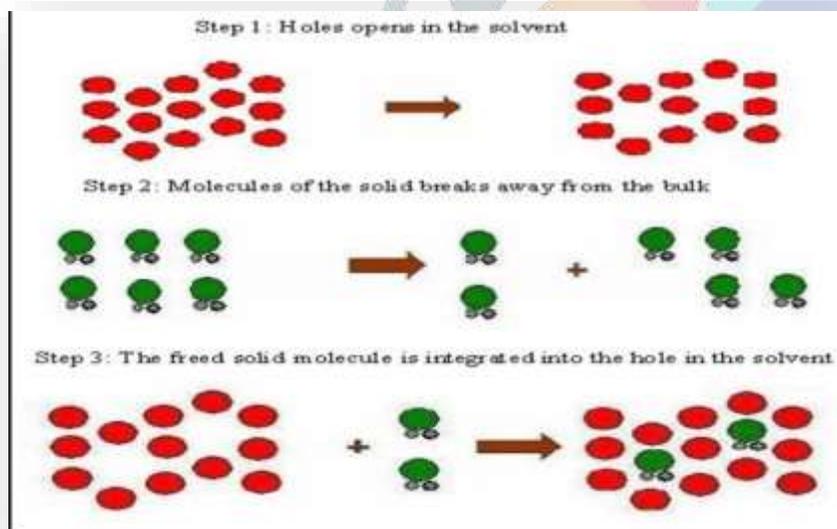


Fig 1:- process of Solubilization

### 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]

### **TECHNIQUES TO OVERCOME POOR SOLUBILITY:-**

**1. Particle size reduction Solubility:** - In this particle size reduction technique, when the particle becomes smaller in size, then the surface area to volume ratio gets increases. The greater surface area allows greater interaction with the solvent which causes an increase in solubility. The poorly soluble drug's bioavailability is related to the particle size of the drug. The surface area which was increased by reducing particle size enhances the properties of dissolution and allows a more range of approaches of formulation and delivery technologies.[12,13]

**a) Particle size reduction by the conventional method:** - Cutting, compression, impact, attrition, and combined impact are various processes involved in the conventional method of size reduction of the particle. Particle size reduction by a conventional method like spray drying and comminution depends upon mechanical stress to disaggregate the active compound. An efficient and economic means of solubility improvement is thus permitting by this size reduction of the particle.

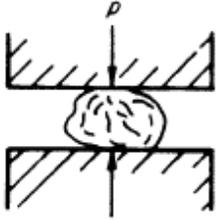
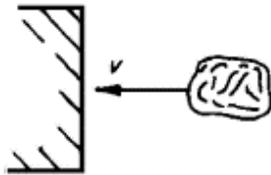
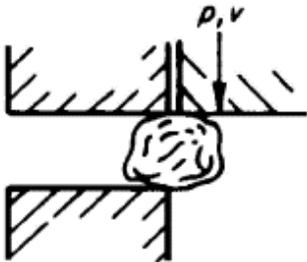
Force	Schematic diagram	Principle	Example of equipment
Compressive		Nutcracker	Crushing rolls
Impact		Hammer	Hammer mill
Attrition		File	Disc attrition mill
Cut		Scissors	Rotary knife cutter

Fig no: 2 forces used in particle size reduction

### “SOLID DISPERSION

Sekiguchi and obi, who researched the dissolution efficiency of eutectic melts of a substance called sulfonamide and water soluble carrier, initially proposed the concept of solid dispersion in the early 1960s [15]. It represents a helpful method used to enhancing the absorption, therapeutic efficacy and dissolution in dosage forms drugs. A collection of solid products composed of at least two distinct compounds usually hydrophilic matrix and hydrophobic drug, then it's referred to as solid dispersion term.

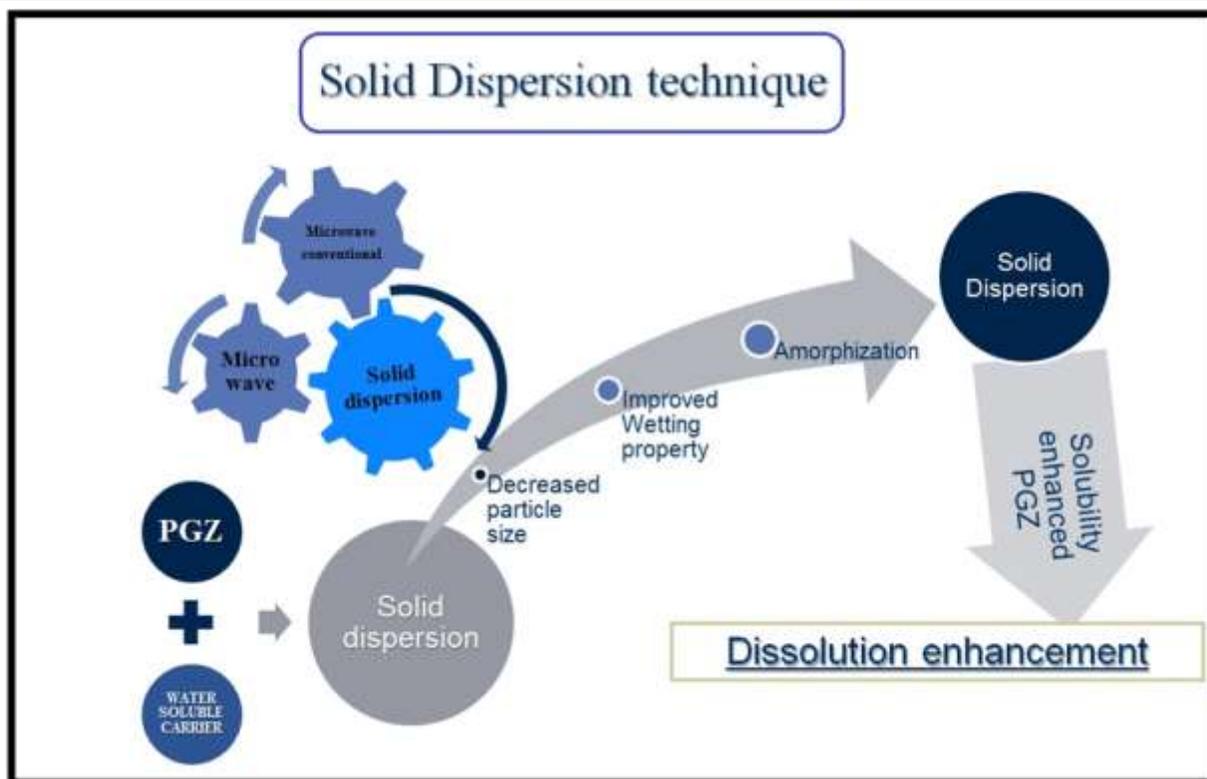


Fig no 3:- solid dispersion technique

Several approaches are used to maximize the aqueous solubility of hydrophobic drugs by solid dispersion such as [16–18]

1. “(fusion method) hot-melt method”
2. “Solvent evaporation method”
3. “Hot-melt extrusion”

### 1. Hot-Melt process (fusion method)

A most common advantage of the hot-melt technique is the economy and ease of it. The hot-melt method is ordinarily investigated by Sekiguchi and Obi to formulate the solid dispersion dosage form with a fast release. In the hot-melt technique, a mixture of a water-soluble carrier and mixture of the drug is directly get heated till then the mixture of both get melts. The melted mixture is then quickly cooled and solidified in an ice bath with intense stirring. With the use of tableting agents, the final mass is then pulverized, crushed, and sieved which can be further compressed into tablets. [19]

The most important requirement for the solid dispersion’s formulation by this method is the drug’s miscibility and the carrier in the molten form.

### 2. “Solvent evaporation method”

The first two to dissolve both the carries and the drugs into natural solvent were Tachibana and Nakamura and under the vacuum, the solvent then gets evaporate to produce a solid solution. It will enable them to produce a solid solution of the highly lipophilic  $\beta$ -carotene in the povidone carrier which is highly water-soluble. Using this method of solvent evaporation, many investigators researched solid dispersion of meloxicam, nimesulide, and naproxen. These results show that the above-mentioned approaches can be successfully utilized to increase the solubility, stability, and solid dispersion of water in-soluble drugs.[22, 24].

This approach needs a higher preparation rate, the choice of the volatile solvent, the complexity of reproducing the crystal forms, and the difficulty in extracting the organic solvent. [21].

### 3. “Hot-melt extrusion”

Hot-melt extrusion operates the same way as the fusion process. In hot-melt extrusion, however, the combining of components is carried out by the extruder. Problems have emerged the miscibility of the drug and the matrix in the common fusion process. High temperatures created by high-shear forces in the extruder are a concern for heat sensitive material in this method of technique. [20].

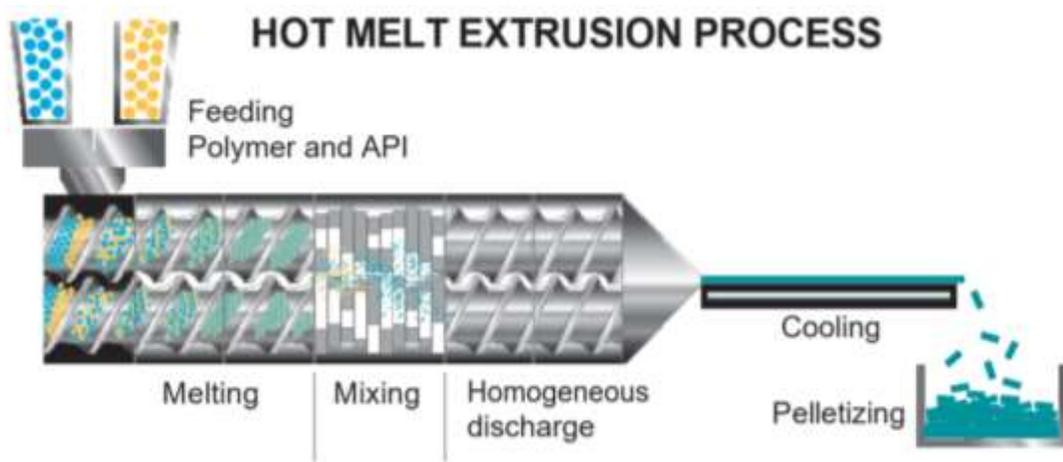


Fig no 4:- hot-melt extrusion process

### HYDROTROPY

This is a process of Solubilization, in which the addition of the second solute with a large amount, the water solubility of the first solute gets increases by the hydrotropic agents. Hydrotropic agents are ionic organic salts this organic salt contains various organic acid and alkali metal salts. Various salts contain more cations and anions that are soluble with each other result in “salting in” of nonelectrolytes is known as “hydrotropic salts”, and this process is also called “hydrotropism. Several additives are used to increase the solubility in water. By use of the hydrotropic agent such as sodium acetate, sodium benzoate, urea, used for complexation to increase the solubility. [24, 25].

Hydrotropes with cationic hydrotropes are found very rare such as - Aromatic amines salt, procaine hydrochloride. When increase the water solubility of the compound by any process of Solubilization they produce the effects such as surfactant aggregation, micelle formation, clouding of polymers, and surfactants. [27].

### pH Adjustment

Drugs that are not soluble in water with molecules parts that can be acid or base are dissolved by applying pH change. pH is adjusted for parenteral and oral both formulation. Blood is the strong buffer with pH 7.2 – 7.4 so the water-insoluble drug may be precipitated in intravenous administration. For the appropriateness of these approaches, the tolerability and buffer capacity is important to select the pH. The pH of the stomach is 1-2 and the pH of the duodenum is 5-7.5 so for the oral administration, the degree of solubility is influenced when the drug passes through the intestines. So pH adjustment is an important approach for oral drug administration...

## Advantages

1. pH adjustment is Simple to analyze formulate.
2. Simple to fast track and to produce.
3. These approaches use small quantities of the compound. [28].

## Canonization

In this approaches powder form of the drug change into nanocrystals in the range 200- 600nm for example amphotericin B. In this method nanocrystals of the drugs are produced and dispersion of drug nanocrystals in a liquid such as water , called nanosuspension.

In order to prepare nanoparticles, three basic techniques are currently use:

- 1.” Pearl milling.”
2. “In water homogenization (wet milling as in a colloid mill) .
3. “Homogenisation of water-miscible liquids in nonaqueous media”. [29].

## CONCLUSION: -

In this review article, we conclude that the solubility of any compound is very important and make an important role in the formulation and drug development. All the above-mentioned techniques or methods which can be used alone or in any combination with others help in improve or enhance the solubility of the compound or any poor soluble drugs. By increase, solubility also increases compliance with patients and also increases the less soluble drug's bioavailability. The selection of any method for improving the solubility is depended upon nature, characteristics of the drug such as chemical nature, physical nature, pharmacokinetic behavior, etc.

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