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Review Paper

A Review on Techniques to Enhance Solubility of Poorly Aqueous Soluble Drug

Vaishnavi Ramavat[1]*, Mangesh Gadekar[2], R. Pagore[3], K. Biyani[4]

[1,2,3], Department Of Pharmaceutics, Karmayogi Tatyasaheb Bondre Institute Of Pharmacy, Chikhli dist. 4 Buldhana, Maharashtra (India) – 443201
[4]Anuradha Collage Of Pharmacy, Chikhli Dist. Buldhana, Maharashtra (India) – 443201.

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ABSTRACT

One of the key factors in achieving the required drug concentration in the systemic circulation for pharmacological response is solubility, which is the phenomenon of a solid dissolving in a liquid phase to produce a homogenous system. A drug's bioavailability and pharmaceutical development are hampered by poor water solubility. More than 40% of novel chemical entities have inadequate bioavailability and poor solubility. These medications fall within BCS class II, which is characterized by high permeability and poor solubility. The biggest problem facing formulation scientists is the behavior of medication solubility. Since their bioavailability is mostly dependent on the dissolution process in the GIT, poorly water-soluble medications have been demonstrated to be slowly and unexpectedly absorbed when taken orally. Therefore, hydrotropy, co-crystallization, co-solvency, salt creation, complexation, and solid dispersion are some of the methods utilized to improve the solubility of poorly soluble drugs in water. Several methods for improving the solubility of medications that are poorly soluble in water are highlighted in this review article

INTRODUCTION

The therapeutic efficacy of a medicine depends not only on its bioavailability but also on the solubility of its molecules. Medication solubility is the highest concentration of the medication dissolved in the solvent under certain condition of temperature, pH and pressure. As solubility is a significant determinant in drug liberation consequently it plays a major function in its bioavailability. For absorption of any medicine it must be present in the form of an aqueous solution at the site of absorption. About 40% of all novel chemical entities have low bioavailability. The

***Corresponding Author:** Vaishnavi Ramavat
Address: *Department Of Pharmaceutics, Karmayogi Tatyasaheb Bondre Institute Of Pharmacy, Chikhli dist. 4 4Buldhana, Maharashtra (India) – 443201.*
Email ✉: ramavatvaishnavi@gmail.com
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bioavailability can be raised by modifications in disintegration and dissolution. Aqueous solubility smaller than 1 µg/ml will undoubtedly produce a bioavailability problem and will influences the efficacy of the medicine. There are number of methods through which aqueous solubility of the drug can be increased. Especially for class II substances according to the Bio pharmaceutics Classification System (BCS), the bioavailability may be improved by raising the solubility and dissolution rate of the drug in the gastro-intestinal fluids [1].

TABLE NO: 1 Solubility Expression

Definition	Parts of solvent required for one part of solute
Very soluble	Less than 1
Freely soluble	From 1 -10
Soluble	From 10 -30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000 -10,000
Insoluble	Greater than 10,000

Biopharmaceutics classification system (BCS)

The system was created by the US Food and Drug Administration (FDA) and classifies medications into four groups based on their solubility and permeability. Due to low solubility, dissolution is the rate-limiting step for drug absorption in Class II and Class IV systems.

TABLE NO: 2 BCS Classification of Drug [2].

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

Process of solubilisation

The process of solubilization involves the solute's inter-ionic or intermolecular bonds being broken, the solvent's molecules being separated to make room for the solute, and interactions between the solvent and the solute molecule or ion. As illustrated in Figure 1, holes appear when the solute binding breaks down during the solubilization process. As seen in Figure 2, solid molecules disintegrate during the solubilization process due to the disruption of intermolecular bonds. The solvent seen in Figure 3 incorporates the liberated solid molecule. [3].

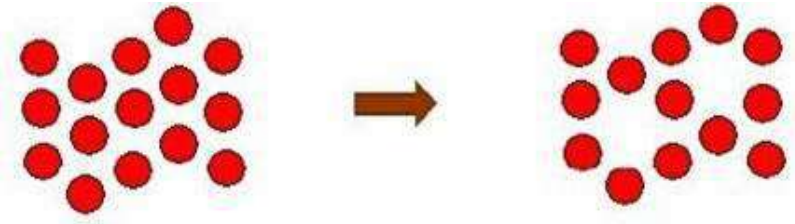

Fig. 1: Holes opens in the solvent

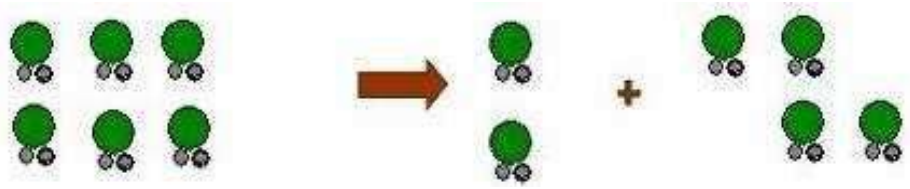

Fig. 2: Molecules of the solid breaks away from the bulk

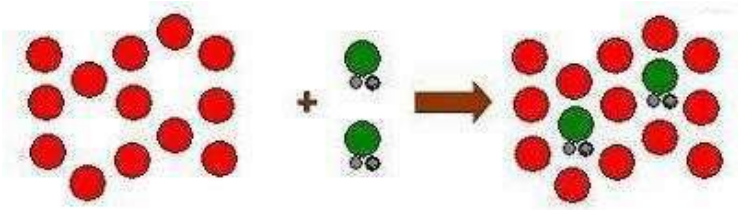

Fig. 3: The freed solid molecule is integrated into the hole in the solvent

Factor affecting

Factor affecting solubility

1. **Chemical Nature of Substance:**
   Chemical Structure, including molecular size, shape and functional groups influences the solubility factor of drugs.
2. **Temperature**:
   Most of the substances dissolves easily in hot liquids as compared to cold liquids.
3. **Pressure:**
   Pressure affects the solubility of gases in liquids, as the pressure is increased solubility is increased.
4. **pH:**
   Solubility of substance sometimes increases or decreases depending upon the pH of the medium.
5. **Concentration:**
   Increase in the concentration of substance leads to an increase in solubility.
6. **Polarity:**
   Polar substances dissolve easily in polar solvents and non-polar dissolves easily in non-polar solvents, "like dissolves like".
7. **Presence of other substances:**
   It can affect the solubility as they can compete for solute-solvent interactions or can form complex with the solute.
8. **Surface Area:**
   Increase in surface area leads to an increase in solubility [4].

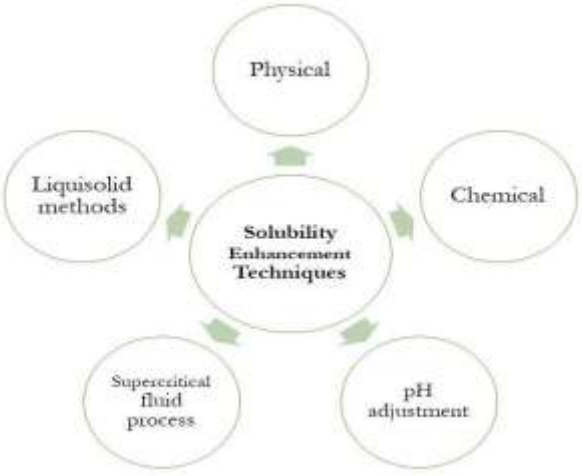

Fig. 4: Broad classification of solubility enhancement techniques [5]

TABLE NO: 3 TECHNIQUES TO OVERCOME POOR SOLUBILITY [6]

I. Chemical Modification Techniques	Salt formation	Conversion of drug into more soluble salt form
	Co-crystallization	Drug–co-former co-crystals
	Co-solvency	Use of water-miscible organic solvents
	Hydrotropy	Use of hydrotropic agents
	Novel solubilizers	Cyclodextrins, polymeric solubilizers
	Nanotechnology-based modification	Drug nanoparticles, nanocarriers
II. Physical Modification Techniques	Particle size reduction	Conventional milling, Micronization
	Crystal habit modification	Polymorphs, Pseudopolymorphs
	Nanosuspensions	Drug nanocrystals stabilized by surfactants
III. Complexation Techniques	Physical mixture	Simple blending with complexing agents
	Kneading method	Wet massing and drying
	Co-precipitation method	Simultaneous precipitation of drug and carrier
IV. Inclusion Complexation Techniques	Kneading method	Cyclodextrin-based complexes
	Lyophilization / Freeze drying	Molecular level dispersion
	Microwave irradiation	Rapid complex formation
V. Surfactant-Based Solubilization	Microemulsions	Thermodynamically stable systems
	SMEDDS	Self-microemulsifying drug delivery systems
VI. Drug Dispersion in Carriers	Solid solutions	Molecular dispersion in solid carrier
	Solid dispersions	Fusion method
		Solvent evaporation method
		Fusion-solvent method
		Spray drying
		Lyophilization / Spray freeze drying
		Hot-melt extrusion
		Dropping method
VII. pH Modification Techniques	pH adjustment	Ionization-based solubility enhancement
VIII. Supercritical Fluid Technology	SCF processing	Supercritical CO_2 based particle engineering
IX. Liquisolid Technique	Liquisolid systems	Drug dissolved in non-volatile solvent and converted to solid
X. Polymeric Alteration Techniques	Polymeric modification	Use of hydrophilic polymers and polymeric carriers

I. Chemical modification

Co-solvency

Drugs that are poorly soluble in water can be made more soluble by combining them with a water-miscible solvent in which they dissolve easily. The solvent employed in combination is referred to as a co-solvent, and this process is called co-solvency. The co-solvent system functions by

lowering the interfacial tension between the hydrophobic solute and aqueous solution. The addition of an organic co-solvent to water causes a significant shift in the solubility of medications; this process is also known as solvent blending. The hydrogen acceptor or donor groups in the co-solvents have a little hydrocarbon area. 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 ensures water solubility [7].

Nanotechnology Approaches:

Drugs with low solubility will be improved by the application of nanotechnology. The study and application of materials and structures at the nanoscale level of roughly 100 nanometers (nm) or less are collectively referred to as nanotechnology. Because micronized products have very little effective surface area for dispersion, oral bioavailability improvement via micronization is insufficient for many new chemical entities with very low solubility. Nanonization is the next phase [8].

Co-crystallization

The use of co-crystals, also known as molecular complexes, is an innovative approach to enhance medication solubility. A solvent may be referred to as a co-crystal if it forms at least two component crystals and is an essential component of the network structure. The solvent is referred to as clathrate (inclusion complex) if it does not actively participate in the network itself, as in open framework structures. A crystalline material made up of two or more molecular (and electrically neutral) species bound together by non-covalent forces is known as a co-crystal. Because the co-crystallizing agents are solids at room temperature, co-crystals are more stable [9].

Salt Formation

Salts have improved solubility and dissolution characteristics in comparison to original drug. The minimum three unit difference between pKa value of the group and that of its counter ions required to form stable salt. Alkali metals salt of acidic drug like penicillin and strong acid salt of basic drug like atropine are more stable than parent drug [10].

II. Physical modification:

Particle size reduction

Particle size reduction can be achieved by micronisation and Nano suspension. Each technique utilizes different equipments for reduction of the particle size.

Nano suspension

Nano suspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilized by surfactants. The advantages offered by Nano suspension increased dissolution rate is due to larger surface area exposed, while absence of Ostwald ripening is due to the uniform and narrow particle size range obtained, which eliminates the concentration gradient facts.

Micronization

The solubility of drug is often intrinsically related to drug particle size. By reducing the particle size, the increased surface area improves the dissolution properties of the drug. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. The micronization is used to increased surface area for dissolution". Micronization does not improve equilibrium solubility; instead, it enhances the rate at which pharmaceuticals dissolve by increasing their surface area. Drug micronization is accomplished through the use of jet mills and rotor stator colloid mills. Eat, because micronization does not alter the drug's saturation solubility, it is

not appropriate for medications with high dosage numbers [11].

Techniques for Micronization

a. Jet milling/fluid energy mill or micronizer
b. Rotor stator colloids mills
c. Micro precipitation & micro crystallization
d. Controlled crystallization
e. Supercritical fluid technology
f. Spray freezing in to liquid

Modification of the crystal habit

a. Polymorphs

b. Pseudopolymorphs

The ability of an element or compound to crystallize in multiple crystalline forms is known as polymorphism. Unique. Despite having the same chemical makeup, drug polymorphs differ in their solubility, melting point, density, texture, and stability, among other physical characteristics. Similarly, a drug's amorphous form is always preferable to its crystalline form because of its increased surface area and higher associated energy. Order for drug dissolution in various solid forms Metastable polymorph > Amorphous Stable polymorphism [12].

III. Complexation:

Complexation is the association between two or more molecules to form a non-bonded entity with a well-defined stoichiometry. It relies on relatively weak forces such as London. Forces, hydrogen bonding and hydrophobic interactions. There are many types of complexing agents

TABLE NO: 4 LIST OF COMPLEXING AGENT

TYPE	EXAMPLES
Inorganic	Ib
Coordination	Hexamine Cobalt (III) Chloride
Chelates	EDTA, EGTA
Metal-Olefin	Ferrocene
Inclusion	Cyclodextrins, Choleic acid
Molecular Complexes	Polymers

Staching Complexation:

These are formed by the overlap of the planar regions of aromatic molecules. Non polar moieties tend to be squeezed out of water by the strong hydrogen bonding interactions of water. This cause some molecules to minimize the contact with water by aggregation of their hydrocarbon moieties. This aggregation is favoured by large planar non polar regions in the molecule stached complexes can be homogenous (self-association) or mixed (complexation) eg., Nicotinamide, Anthracene, Pyrene, Methylene Blue [13].

IV. Inclusion Complexation

This is most widely used method to enhance water solubility and increase stability of hydrophobic drugs by using cyclodextrins. Solid inclusion complexes can be prepared by using following methods.

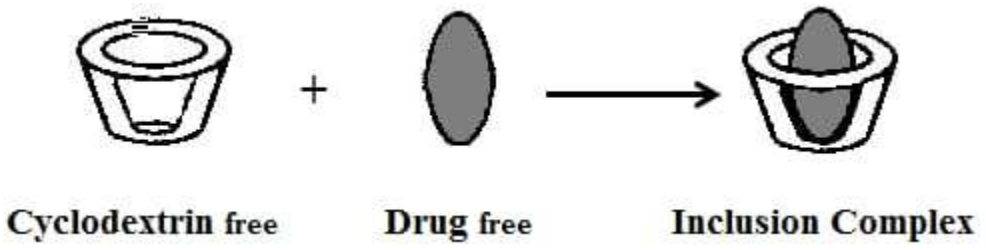

Fig. 5: CD-Drug complex

a. Kneading Technique

This method is based on impregnating the CDs with little amount of water or hydro alcoholic solutions to converted into a paste. The drug is then added to the above paste and kneaded for a specified time. The kneaded mixture is then dried and passed through sieve if required [14].

b. Lyophilization/Freeze-Drying Technique:

This procedure, which can also be called a substitute for solvent evaporation, involves the molecular mixing of medication and solvent in a shared solvent. Water's special ability to function as a solvent, gas, diluent, plasticizer, and stabilizer is essential to lyophilization. Using this technique, the drug and cyclodextrin-containing solution is first frozen and then dried at low pressure to remove the solvent system.

c. Microwave Irradiation Method:

This technique uses a microwave oven to create a microwave irradiation reaction between the complicated agent and the medication. In R.B.F., the medication and cyclodextrin are combined in a solution of organic solvent and water in a predetermined molar ratio. Next, the reaction is started in a microwave at 60°C for one to two minutes. After the reaction is finished, enough solution is added to eliminate the remaining, uncomplexed free medication and cyclodextrin. The precipitate is then filtered using Whatman filter paper and dried for 48 hours at 40°C in a vacuum oven [15].

V. Solublaization by surfactant

1. Micro Emulsion:

Micro emulsion is known as a system of water oil which thermodynamically stable liquid solution. A micro emulsion can be divided of four component system such as internal phase, external phase, surfactant and Co-surfactant, Non-sonic surfactant like labrafil and tweens with high hydrophile-lipophlie balances which are used to formation of oil-in water droplets during the production In micro emulsion technique, many equipment are used such bath, stirring rod, volumetric flask and homogenizer Micro emulsion is known as the isotropic, clear pre concentrate, thermodynamically stable translucent system which is containing a mixture of oil, hydrophilic solvent and hydrophilic surfactant dissolved in a poorly water soluble drug [16].

2. Self-emulsifying drug delivery systems

Uses the concept of in-situ development of emulsion in the gastrointestinal tract. The mixture of oil, co-surfactant, surfactant one or more hydrophilic solvents and co- solvent forms a transparent isotropic solution that is known as the self-emulsifying drug delivery system (SEDDS). Self-emulsifying drug delivery systems (SEDDS) and self microemulsifying drug delivery systems (SMEDDS) are isotropic solutions of oil and surfactant which form oil-in-water microemulsions on minor agitation in the presence of water. These new colloidal preparations on oral

administration act like oil-in-water microemulsions [17].

VI. Drug dispersion in carriers

Solid dispersion

In the early 1960s, Sekiguchi and Obi developed the idea of solid dispersions by examining the production and dissolution capabilities of eutectic melts of a sulphonamide medication and a water-soluble carrier. One practical pharmaceutical method for improving the dissolution, absorption, and therapeutic efficacy of medications in dose forms is the use of solid dispersions. A collection of solid goods made up of at least two distinct components—typically a hydrophilic matrix and a hydrophobic drug—are referred to as solid dispersions. Solid dispersions of polyvinylpyrrolidone (Povidone, PVP), polyethylene glycols (PEGs), and Plasdone $630 are the most used hydrophilic carriers. Solid dispersion formulations also include surfactants such as Tween-80, docusate sodium, Myrj-52, Pluronic-F68, and sodium lauryl sulphate (SLS) and ritonavir can be enhanced by solid dispersion with appropriate hydrophilic carriers, such as ritonavir with gelucire and celecoxib with povidone (PVP) [18].

Manufacturing methods of solid dispersion

Solvent evaporation method: In the solvent evaporation method, the medication and carrier are dissolved in a common solvent, which is then evaporated under vacuum to create a solid solution. The medicine (B-carotene) and its carrier (PVP) were initially dissolved in a common solvent by Tachibechi and Nakumara. To create a solid dispersion, evaporate the solvent under vacuum. Solvents like ethanol, chloroform, or a combination of ethanol and dichloromethane are frequently used. In certain situations, cosolvant may be used since it may be necessary to employ a lot of solvents and heat in order to completely dissolve the medicine and carrier. The primary benefit of the solvent approach is that, due to the comparatively low temperatures needed for the evaporation of organic solvents, thermal breakdown of medications or carriers can be avoided. The disadvantages of the solvent approach include the following: it is costly, environmentally harmful, and challenging to locate common and removable solvents; it is difficult to fully remove liquid solvent; and it is challenging to replicate crystal form.

1. **Fusion/melting method:** A drug and a water-soluble carrier were physically combined and heated until they melted. After that, the melted fluid was quickly cooled and solidified in an ice bath while stirring continuously. The drug's solubility and bioavailability were enhanced by breaking down, grinding, and sieving the final solid mass. This method's drawback is that many drugs may disintegrate at high temperatures.

2. **Hot melt extrusion:** 10-30 HME can be summarized up as the process of creating a new material ("extrusion") by putting it through a die or orifice under carefully regulated parameters like temperature, mixing, feed rate, and pressure. In contrast to simple extrusion, HME requires no solvents for granulation because polymer, drug, and excipient blends are thoroughly combined in the molten state. The thermal binder is the molten polymer. [19].

3. **Fusion-Solvent Method:** Fusion processes involve melting a carrier or carriers and incorporating the medication or drugs as a solution. Solvent removal is not required if the liquid is harmless and the carrier may hold a particular quantity of liquid while retaining its solid qualities. Otherwise, this approach is

subject to the same solvent retention criticism already mentioned. This approach is especially helpful for medications that are thermolabile or have high melting points. The method's viability has been proven for griseofulvin and spironolactone dispersions in polyethylene glycol 6000 [20].

VII. PH adjustment

If the pH varies, a medication that is poorly soluble in water might dissolve. When obtaining solubility using this method, the buffer capacity and tolerance of the selected pH must be taken into account. 1961 Drug solubility is increased by excipients that raise the pH of the environment in the dosage form to a level higher than the pKa of weekly acidic medications; weekly basic medications may be made more soluble by excipients that act as alkalizing agents. It can also be applied to lipophilic and crystalline weakly soluble materials [21].

VIII. Supercritical fluid process

This technology has been introduced in late 1980s and early 1990s. Since the first experience of Hannay et al., in 1879, a number of techniques has been developed and patented in the field of SCF process. SCF technique can be applied to the preparation of solvent-free solid dispersion dosage form to enhance the solubility of poorly soluble compounds. A solid dispersion of Carbamazepine in polyethylene glycol (PEG) 4000 increased the rate and extended the dissolution of Carbamazepine. In this method, a precipitation vessel was loaded with solution of Carbamazepine and PEG-4000 in acetone, which was expanded with supercritical CO_2 from the bottom of the vessel to obtain solvent-free particles. SCFs either as solvent: Rapid expansion from supercritical solution (RESS) or as antisolvent: Gas antisolvent (GAS) and supercritical antisolvent (SAS) [22].

IX. Liquisolid Technique:

This system is refers to the Formulations which is formed because of the liquid drugs, drug solution or drug suspension in a nonvolatile solvent into a Dry, Free flowing, Non adherent and a Compressible powder as well as stable Mixture by blending the suspension or solution, using the suitable carriers and coating materials. There are various grades of starch, Lactose and cellulose available and that can be used as a Carrier. Also Silica powder may be used as a good coating material by using a very fine grade. The process of emulsification which increases surface area of particles and that can leads to increase in the drug release profile from the suitable vehicle. In this the surfactant play an Imp. Role which can mimic the formation of micelles in a bile salts and because of this solubility characteristics of poorly water soluble drug is increases. The Rate and Extent of absorption of drug is affected if the dissolution as well as solubilization characteristics of hydrophobic drug are changed [23].

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