



## Review Article

### REVIEW ON SOLUBILITY: A MANDATORY TOOL FOR PHARMACEUTICALS

Keshav Jindal \*

Department of Pharmaceutics, Chandigarh University, Gharuan, Distt. Mohali, Punjab, India

\*Corresponding Author Email: keshav208@gmail.com

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#### ABSTRACT

Solubility of drug substance is a major issue in Pharmaceutical area. If drug product is to be administered orally in solid form, then it is mandatory that the drug product must solubilized within the gastro-intestinal fluid prior to absorption, and if drug product fails to do so then the patient will not achieve the required therapeutic effect. Now-a-days solubility is a major issue for Pharmaceutical dosage forms. Almost 30% to 40% of the upcoming drug substances have low water solubility. Solubility of pharmaceutical products defines the bioavailability and absorption of a drug. By improving solubility, the dissolution behavior of any drug can also be improved. Therapeutic effectiveness of drug product depends on its bioavailability, and ultimately on solubility of the drug product.

**Keywords:** Solubility, drug, dosage form, bioavailability, absorption

#### INTRODUCTION

Solubility is an intrinsic property of any dosage form, i.e. properties of active compound can be improved by internal modification i.e. by complexation of poorly soluble compounds with water soluble carrier. On the other hand dissolution is an extrinsic property of drug product, wherein properties or nature of active compound can be improved by external modification i.e. by size reduction, due to which effective surface area of active component will be increased and enables more contact with intestinal fluids for better absorption of drug. Solubility of drug product can be defined as both quantitatively and qualitatively.

**Quantitative solubility** is defined as that milligram of solute particles required to make a saturated solution.

**Qualitative solubility** is defined as where two phases are mixed together to form a homogenous solution. With the introduction of combinatorial chemistry and high throughput screening the properties of new developed active compound shifted towards higher molecular weight and lipophilicity of compound is increased, and this results in a decrease in aqueous solubility of compound.

There are some aspects where active compound possesses low solubility.

- Active compound having five or more than five number of carbon atoms
- Value of log P is two or greater than two
- Molecular weight of compound is greater than 500 Daltons

These above mentioned aspects are referred to as **Lipinski rule**, which demonstrate active compound as non-aqueous or poorly aqueous soluble.

Solubility of drug substance can be altered on two levels either through material engineering of drug substance or through formulation approaches.

Besides aqueous solubility, permeability is another critical aspect for oral bioavailability.

The Biopharmaceutical Classification System (BCS) was introduced in the mid 1990's to classify the drug substances with respect to their aqueous solubility and membrane permeability<sup>1</sup>.

**Table 1: Drugs are classified as BCS-I to BCS-IV**

Classification	Property
BCS-I	Highly Soluble, Highly Permeable
BCS-II	Low Soluble, Highly Permeable
BCS-III	Highly Soluble, Low Permeable
BCS-IV	Low Soluble, Low Permeable

It is very challenging task to improve parameters for drugs belonging to BCS-IV.

It takes into account that low dose of drug product belonging to BCS-II or BCS-IV is soluble in intestinal fluid while at high dose similar drug product is not dissolved or solubilized in intestinal fluid. On account of this different Pharmacopoeias (IP, USP and BP) give some definitions for solubility<sup>2</sup> as given in table 2.

**Table 2: Solubility criteria**

Description	Parts of solvent required for one part of solute
Very soluble	Less than 1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10000
Insoluble	More than 10000

Description for "Insoluble" is not mentioned in European Pharmacopoeia.

## TECHNIQUES TO ENHANCE SOLUBILITY

### Physical modification

#### Particle size reduction

Micronization  
Sonocrystallization  
Nano-suspension  
Super critical fluid process

#### Modification of crystal habit

Polymorphism  
Pseudo polymorphism

#### Drug dispersed in carriers

Eutectic mixtures  
Solid dispersion

#### Complexation

Using complexing agents

#### Solubilization by surfactants

Micro emulsions

#### Chemical modification

Change in pH  
Use of buffer  
Derivatization

#### Other methods

Co-crystallization  
Co-solvency  
Hydrotrophy  
Solubilizing agents  
Selective adsorption on insoluble carrier  
Solvent deposition  
Using soluble prodrug  
Functional polymer technology

## PHYSICAL MODIFICATION TECHNIQUES

### Particle size reduction

**Micronization-** It decreases dissolution rate of drug by increasing surface area. Micronization of drug is done by milling technique using jet mill, rotor mill, and colloidal mill.

Micronization is not suitable for drugs having high dose number ( $D_0$ ). Solubility of sex steroid i.e. Estradiol may be enhanced by micronization technique<sup>3</sup>.

Dose number is defined as volume of bio-relevant media per kilogram of animal or human being that would be needed to completely dissolve the dose.

If drug substance is having dose number greater than one then it is less soluble and if dose number of drug substance is less than one then it is more soluble.

**Nano suspension-** These are submicron colloidal dispersion of drug which are stabilized by surfactants. Particle size distribution is less than 1 micrometer and average particle size ranges between 200-600 nm.

Research is going on some compounds viz. Paclitaxel, Amphotericin-B and Tarazepide<sup>4</sup>.

**Sonocrystallization-** A process in which the particle size reduction takes place through crystallization by sonication is called as sonocrystallization.

Sonocrystallization results in size reduction and controlled size distribution. Sonocrystallization is an application of ultrasound energy to control the nucleation of crystallization process. Applying ultrasound to crystallization results in nucleation at the lowest level of super-saturation where the crystallization overcomes the tendency of the compound to re-dissolve in the solution. This process is generally employed on inhalation dosage form.

**Super critical fluids (SCF)** - These are very dense and non-condensable fluids whose temperature and pressure are greater than critical temperature and critical pressure. These possess properties of both liquids and gases. Favorable characteristics of gases are high diffusibility, low surface tension and low viscosity to control the solubilization of drug with super critical fluid.

#### DRUG + SCF DRUG WITH REDUCED PARTICLE SIZE

SCF allows micronization of drug particle often to sub-micron ranges. As a result the particle size of drug will be reduced, effective surface area of drug with biological fluids will increase which results in greater dissolution of drug in biological fluid, and hence the better solubility of drug substances.

Solubility of 5-Fluorouracil,  $\alpha$ -chemo trypsin (in sub-micron range) and Amoxicillin may be enhanced by SCF method<sup>5</sup>.

### Modification of crystal habit

**Polymorphism-** It is defined as that crystallinity of substance which exists in more than one form.

Polymorphism shown by pharmaceutical substance is of two types i.e. Enantiotropic (one form of polymer can change in other form) and Monotropic (no reversible transition is possible).

Amorphous substance have greater hydration energy than crystalline substances, due to this greater hydration energy they tends to shows more solubility than crystalline substances.

Metastable state is a state in between the crystalline state and amorphous state of powder. Therefore order of solubility for Pharmaceutical powders is:

Amorphous > Metastable > Crystalline.

**Pseudo polymorphism-** When crystalline form of drug is incorporated in solvent, it is called as solvates, and when water is used as solvent to incorporate a crystalline lattice then it is called hydrate.

Existence of this solvate or hydrates in different crystalline forms is called pseudo polymorphism.

Generally hydrates are already in interaction with water and they have less energy for crystal breakup thus shows less solubility when compared to anhydrous forms. For example, the antidiabetic drug Glibenclamide, orally used sulfonylurea has been isolated as solvates using organic solvents i.e. pentane and toluene which exhibited higher solubility and dissolution rate than non-solvated polymorphs<sup>6</sup>.

### Drug dispersion in carriers

In this technique drug is dispersed inside an inert carrier system in solid or powder form, called solid dispersion. This process can be carried out by three methods:

**Hot melt method-** In this method drug is to be mixed with an organic solvent followed by heating of mixture of drug and organic solvent which is then followed by rapid cooling; resultant will form a solid dispersion with enhanced solubility. Condition for this method is that drug should be thermostable or drug should withstand higher and lower temperature.

**Solvent evaporation method-** In this method drug is mixed in an inert vehicle and this mixture is to be incorporated in organic solvent, in which mixture of drug and vehicle is having solubility; resultant of this will form a solution, followed by evaporation of an organic solvent. Evaporation of an organic solvent is to be carried by freeze drying, followed by precipitation of mixture and resultant will be a solid dispersion.

**Hot melt extrusion method-** In this method the drug, polymer and excipients are to be mixed together in molten form and there is no need of any vehicle or organic solvent for this technique<sup>7</sup>.

**Eutectic mixtures-** Eutectic mixture consist of two compounds which are completely miscible in liquid state but to a limited extent in solid state. When the mixture is cooled both crystallize out spontaneously.

Solid eutectic mixtures are usually prepared by cooling of co-melt of two compounds in order to obtain fine mixture of both compounds.

When eutectic mixtures are exposed to gastrointestinal fluids, the soluble carrier dissolves rapidly. The large surface area should result in enhanced dissolution rate thereby improved bioavailability. Eutectic mixture prepared with hydrophilic agent also increase solubility of drugs.

Eutectic combination of chloramphenicol/urea and sulfathiazole/urea increased the solubility of poorly soluble drug.

**Complexation-** Complexation is association between two or more molecules to form a non-bonded entity. In complexation generally weak forces are involved i.e. London forces, hydrogen bonding and hydrophobic interactions.

There are two types of complexes available:

**Stacking complexes-** This is a process to make the complex between two moieties with the help of  $\pi$ - $\pi$  interaction i.e. caffeine form a complex with a neurotoxin (MPTP [1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine], responsible to cause Parkinson like condition). Caffeine itself is not up taken by the neurons, but by forming stacking complex between caffeine and MPTP, caffeine is up taken by neurons and this condition may be prevented by preventing the blocking of adenosine receptors.

**Inclusion complexes-** This is a process to form a complex by incorporating non-polar molecule in the cavity of another molecule. There are no forces and no bonds are associated between them, therefore these complexes are called non-bonded complexes. Cyclodextrins (cyclic oligosaccharides obtained from the enzymatic degradation of starch) are solely responsible to form the inclusion complexes. Three types of Cyclodextrins (CD) are available, i.e.  $\alpha$  CD with six D-glucopyranose units,  $\beta$  CD with seven D-glucopyranose units and  $\gamma$  CD with eight D-glucopyranose units.

Cyclodextrins possess their structure with hydrophilic exterior and less hydrophilic interior. Cyclodextrins are generally used to improve the solubility and bioavailability of poor water soluble drugs. Cyclodextrins are never used in pure forms while they combine with hydroxyl propyl groups to impart their maximum water soluble activity, i.e. hydroxyl propyl- $\alpha$ -cyclodextrin (HP- $\alpha$ -CD), hydroxyl propyl- $\beta$ -cyclodextrin (HP- $\beta$ -CD) and hydroxyl propyl- $\gamma$ -cyclodextrin (HP- $\gamma$ -CD). HP- $\beta$ -CD is most commonly used in pharmaceutical preparations.

#### Solubilization by surfactants

Surfactants are designated with distinct polar and non-polar region. In most surfactants hydrocarbon portion connects with polar group. Polar group may be ionic, cationic, zwitter ion or

non-ionic. Surfactants enhance solubility of drugs by reducing the surface tension between drug and solvent.

**Micro emulsions-** Generally it is four component systems which consist of an external phase, internal phase, surfactant and co-surfactant. Surfactant is soluble with internal phase of the system which makes a clear, isotropic and thermodynamic stable system called micro emulsion. Droplet diameter of internal phase of micro emulsion is  $< 0.1\mu\text{m}$ .

#### CHEMICAL MODIFICATION TECHNIQUES

**By changing pH-** Generally the condition for the absorption of dosage form is to be remained in un-ionized form, sometimes the drug is not soluble in GIT (constitute stomach, small and large intestine) fluids and solubility is the prime criteria for the absorption of drug, hence to increase the solubility there is a need to bring change in pH of drug candidate.

If drug is of higher pH it will be soluble or ionizable in gastric fluid and if drug is of lower pH it will be soluble in intestinal fluid.

**Use of Buffers-** Generally dilution of GIT fluid may have an effect on the solubility of drug. If precipitation of drug occurs by dilution of GIT fluid then solubility of drug will be reduced. This problem may be overcome by use of buffers, which maintain the pH of GIT even in dilution conditions and solubility of drug will be maintained.

**Derivatization-** In this technique parent form of poorly soluble drug is to be modified into a derivative of poorly soluble drug. Derivatization may be achieved by two methods; either by forming a prodrug or forming or changing the salt form of drug.

**Prodrug:** It is a process in which drug moiety is covalently bonded with inert matrix or carrier, because drug itself is not stable outside body and due to less stability drug may be degraded in an external environment. As a result solubility of drug will be diminished. When prodrug is administered, then covalent bond between the drug and inert matrix is broken and drug is available in its parent form inside body or in short term it can be said that prodrug is active inside the body and where drug shows good pharmacological effect with ideal solubility. Cyclophosphamide (anti-cancer drug) is prodrug and its active metabolite in body is 4-hydroxy cyclophosphamide<sup>8</sup>.

**Salt form of drug-** Solubility of drug may be significantly enhanced by forming or changing the salt form of drug e.g. solubility of Clindamycin hydrochloride is 3mg/ml, while it has been changed to Clindamycin phosphate the solubility is significantly changed i.e. 150mg/ml.

#### OTHER METHODS AND TECHNIQUES

**Co-crystallization-** In this technique drug is mixed with an inert (lacking of pharmacological activity) substance in equal molar ratio followed by adding the aqueous solvent in small amount followed by slowly evaporation of aqueous solvent and resultant product will be co-crystals and by which solubility of drug substance is enhanced.

Solubility of Fexofenadine is enhanced by this method. Equal molar ratio (1:1) of Fexofenadine i.e. 501 gm and tartaric acid i.e. 150 gm is to be taken and this mixture is to be added in 10 ml of water and slowly evaporation of water converts this mixture into co-crystals of Fexofenadine and resultant solubility of drug is enhanced.

**Co-solvency-** This method is employed for poorly water soluble drugs. Any external aqueous solvent is to be added in mixture of drug and water and that external solvent increases the solubility of drug in water. This process is called co-solvency and aqueous solvents which are used to enhance solubility are called co-solvents e.g. Poly-ethylene glycol (PEG-400), propylene glycol (PG) and glycerol are used as well-known co-solvents.

Co-solvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly referred to as solvent blending. Most co-solvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen-bonding groups ensure water miscibility, while their hydrophobic hydrocarbon regions interfere with water's hydrogen bonding network, reducing the overall intermolecular attraction of water. Solubility of Etoricoxib can be enhanced by co-solvency technique<sup>9</sup>.

**Hydrotrophy-** Generally these are anionic organic substances which are used to enhance the solubility of poorly aqueous soluble drugs. Hydrotrophs are used at high concentration with poorly soluble drug to enhance solubility parameter.

Structure of Hydrotrophs consists of two parts i.e. hydrophilic part and hydrophobic part and poorly soluble drug is to be interacted with anionic or hydrophilic part of hydrotrophs. Hydrotrophs are also known as non-micelle forming substances and are either liquid or solid in nature.

Urea, sodium citrate, sodium salicylate, potassium acetate and potassium citrate (table 3) are widely used hydrotropic agents to enhance the solubility of poorly soluble drugs<sup>10</sup>.

**Table 3: Examples of hydrotropic drugs**

Drug	Hydrotropic agent
Cefprozil	Potassium citrate and potassium acetate
Paracetamol	Urea
Cefadroxil	Urea
Theophylline	Sodium salicylate
Salicylic acid	Sodium salicylate
Nifedipin	Sodium salicylate
Hydrochlorothiazide	Sodium acetate and urea
Ketoprofen	Sodium citrate and urea

**Solubilizing agents-** In this technique inter molecular forces between the solute or poorly soluble drug particle is broken down by the addition of a solvent and that solvent provides space to incorporate the poorly soluble drug particles. This process is called solubilization<sup>11</sup>.

**Table 4: Examples of Solubilizing agents**

Drug	Solubilizing agent
Hydrochlorothiazide	PEG-400
Nimodipine	Modified gum karaya (MGK)
Halofantrin	Caffeine and nicotinamide

**Selective adsorption on insoluble carrier-** In this method poorly soluble drug is adsorbed on the surface of an inert substance i.e. clay. When adsorbing substance comes in contact with body fluid, then it forms a weak bond with the fluid and swells; resultant is that drug releases in body fluid or dissolution behavior of drug is improved, by which solubility is also enhanced. Bentonite is used as an adsorbing substance to increase the solubility of Indomethacin, Griseofulvin and Prednisolone<sup>12</sup>.

**Solvent deposition-** In this method poorly soluble drug is to be incorporated in an organic solvent and an inert carrier is to be added in mixture of drug and organic solvent. Such examples are given in table 5. This system is to be stirred on magnetic stirrer to make slurry and organic solvent is to be evaporated from this slurry by keeping the mixture on water bath. Temperature of water bath should be just above the boiling point of organic solvent. When organic solvent will be removed, then mixture of drug and carrier is to be placed in vacuum chamber for drying and dried mass is grinded or micronized to make a fine powder; and ultimately solubility of drug will be enhanced<sup>13</sup>.

**Table 5: Examples of carrier drugs**

Drug	Organic solvent	Carrier
Indomethacin	Acetone	Fumed silicon dioxide
Digoxin	Chloroform : methanol (1:1)	Silicon di-oxide
Glibenclamide	Chloroform	Microcrystalline cellulose
Piroxam	Dichloromethane	Microcrystalline cellulose
Chlordiazepoxide	Dichloromethane	Starch-lactose granules

**Using soluble prodrug-** Prodrugs are poorly active or inactive substances which perform in-vivo biotransformation to release the drug in its active metabolite to increase the efficiency of drug. Prodrugs are efficiently used to increase the solubility of poor aqueous soluble drugs. Some examples are given in table 6. For this approach prodrugs will be formed by two ways i.e. carrier linked prodrugs and bio-precursors. Inert moiety form a direct or indirect bond with the poorly soluble drug to form carrier linked prodrug and there is no bond formation with the inactive moiety and poorly soluble drug to form bio-precursors, there is use of spacers (provides a link between the inert moiety and poorly soluble drug).

**Table 6: Examples of soluble prodrugs**

Drug	Actual solubility (in water)	Moiety to be attached with poorly soluble drug	Solubility after forming a prodrug (in water)
Oleanoic acid (Hepatoprotective)	0.012µg/ml	L-Valine	25 µg/ml
Oleanoic acid (Hepatoprotective)	0.012µg/ml	L-Valine+ L-Alanine	>1 mg/ml
Oridonin (Anti-cancer)	Insoluble	Poly-ethylene glycol (PEG) with molecular weight of 5kDa	99 times
Gambogic acid (Anti-cancer)	0.5 mg/ml	Poly-ethylene glycol (PEG) with molecular weight of 2kDa to 20kDa + L-Leucine is used as spacer	645-1750 mg/ml
Paclitaxel (Anti-cancer)	15 µg/ml	O-N intramolecular acyl migration reaction	60 mg/ml (400 times)

**Functional polymer technology-** Polymers play an important role to enhance the bioavailability of drug product. Eudragit derivatives are used to enhance the solubility of poorly soluble drugs i.e. Eudragit E 30D, chemically it is ethyl prop-2-enoate; methyl 2-methylprop-2-enoate and Eudragit E, chemically it is butyl 2-methylprop-2-enoate; 2-(dimethyl amino)ethyl 2-methylprop-2-enoate; methyl 2-methylprop-2-enoate. Eudragit E 30D and Eudragit E are used to enhance the solubility of Femodipine and Carbamazepine<sup>14</sup>.

## CONCLUSION

From the above discussion, it was concluded that the dosage form should be present in solution form at the absorption site for better absorption of drug; if not so, then dosage form will not be soluble with the fluid present at absorption site. Consequently, therapeutic effect from active substance will not be achieved. Hence using the above mentioned techniques, it becomes possible to enhance the solubility of poorly soluble drugs and thus achieve a desired therapeutic effect.

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