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# Drug Solubility: Challenges And Opportunities For Pharmaceutical Development

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**Abstract**

Solubility, the phenomenon of dissolution of solute in solvent to give a homogeneous system, is one of the importance parameters to achieve desired concentration of the solution. The solubility and dissolution of drug in GI fluid is the rate determining step in absorption of drug. Low water solubility is the major problem encountered with the formulation of development of certain new chemicals. There is various technique available for increasing the solubility enhancement techniques of poorly soluble drugs and other techniques like salt formation use of surfactant complexation and so on. Selection of solubility improving methods depends on drug property, site of absorption, and required dosage from characteristics.

**Key-Words:** Solubility, BCS, Drugs, Solvent, Dosage form.

## 1. Introduction

Drug solubility is one of the most important factors in the development of effective pharmaceutical formulations. Solubility is defined as the maximum amount of solute particle which can be dissolved in per 100ml/gm of solvent or the concentration of solute in saturated solution at a certain temperature, pressure or presence of some chemical. It's essential for formulating medications, especially orally administered ones, as a drug must dissolve in the fluids of gastrointestinal tract to be absorbed into the bloodstream. Solubility of the substance are depending on the solvent and also depends on temperature and pressure. Adequate solubility is the essential drugs for a drug to be absorbed, distributed, metabolized, and finally exert its therapeutic effect [1].

However, many newly developed drugs belong to the Biopharmaceutical Classification System (BCS), meaning they suffer from poor aqueous solubility. In the 1990s; the biopharmaceuticals classification system (BCS) was introduced to characterize various drugs according to their solubility and permeability [2]. This poor solubility often leads to low bioavailability, incomplete absorption, and reduced therapeutic efficiency. The extent of solubility ranges widely from infinitely soluble such as ethanol in water to poorly soluble such as silver chloride in water. The term insoluble is often applied to poorly soluble compound. Therefore, improving solubility has become a major challenge in modern drug delivery [3].

## 2. Biopharmaceuticals Classification System (BCS)

The Biopharmaceutics Classification System is a system to differentiate drugs on the basis of their solubility and permeability.

1. Solubility- how easily the drug dissolves in gastrointestinal fluid.
2. Permeability- how easily the dissolved drug passes through biological membranes (likes the intestinal) to reach the bloodstream.

### 2.1 According to BCS, drug solubility is divided into four types:[4]

**Type 1: High Solubility-High Permeability**

- ✓ Drugs dissolve quickly and are well absorbed.
- ✓ Example: Paracetamol, Metoprolol.
- ✓ Usually have good bioavailability.

**Types 2: High Solubility-Low Permeability**

- ✓ Drugs dissolve poorly and do not permeate easily.
- ✓ Examples: Hydrochlorothiazide, Paclitaxel.
- ✓ Most challenging; need advanced drug delivery systems.

**Type3: Low Solubility-High Permeability**

- ✓ Drugs can cross membranes easily but dissolve poorly.
- ✓ Absorption depends on dissolution rate.
- ✓ Example: Ketoprofen, Carbamazepine.
- ✓ Need solubility enhancement techniques.

**Type 4: Low Solubility-Low Permeability**

- ✓ Drugs dissolve poorly and do not permeate easily.
- ✓ Example: Hydrochlorothiazide, Paclitaxel.
- ✓ Most challenging: need advanced drug delivery systems [5].

## 3. Importance of Biopharmaceuticals Classification System (BCS)

- Helps in selecting **drug formulation strategies**.
- Provides basis for **biowaivers** (regulatory approval without in vivo bioequivalence studies for drugs.
- Supports **predicting oral drug absorption.**

**Table 1: Solubility criteria as per B.P, U.S.P. [6]**

| Descriptive Term | Parts of the solvent required per part of solute |
|---|---|
| Very soluble | Less than 1 |
| Freely soluble | From 1 to 10 |
| Soluble | From 10 to 30 |
| Sparingly soluble | From 30 to 100 |
| Slightly soluble | From 100 to 1000 |
| Very Slightly soluble | From 1000 to 10,000 |
| Practically insoluble | 10,000 and over |

### 3.1 Importance of Solubility

Solubility is the ability of a drug to dissolve in a solvent, usually water or biological fluids. In drug development, solubility is extremely important because it directly affects how well a drug in the body. Solubility also play a major role for other dosage forms like parental formulations as well [7].

#### 3.1.1 Drug Absorption and Bioavailability

- For a drug taken orally, it must dissolve in gastrointestinal fluids before it can be absorbed into the bloodstream.
- Poor solubility – poor absorption - low bioavailability.

#### 3.1.2 Therapeutic Effectiveness

- Is a drug doesn't dissolve properly, it cannot reach the required concentration in blood/ plasma.
- This may lead to treatment failure even if the drug itself is potent.

#### 3.1.3 Dose Optimization

- Drugs with good solubility require smaller doses, reducing side effects.
- Poorly soluble drugs may need higher doses, increasing risk of toxicity.

#### 3.1.4 Drug Formulation Design

- Solubility determines the type of dosage form (tablet, capsule, injection, suspension, etc.).
- Injectable drugs require high solubility to ensure safe and effective administration.

#### 3.1.5 Regulatory Approval

- Solubility data is essential for BCS classification and for obtaining biowaivers (approval without extensive clinical trials for highly soluble and permeable drugs).

#### 3.1.6 Patient Compliance

- Good solubility can reduce the number/ frequency of doses, making therapy easier for patient.

### 3.2 Process of Solubilization [8]

1. Breaking of inter-ionic or inter-molecular bonds in the solute, the separation of the molecules of the solvent to provide space for the solute, interaction between solute and solvent molecule.

2. Molecule of the solid breaks away from the bulk.

3. The feed of solid molecule is integrated into the hole in solvent.

### 4. Solubility Enhancement Techniques

These are those techniques which are used to increase the solubility of any drug/solute, if their solubility is less in aqueous medium.

**For increase solubility there are various techniques [7-14]**

- **Chemical Modifications:**
  - I. Salt Formation
  - II. Co-crystallization
  - III. Co-solvency
  - IV. Hydrotropy
  - V. Use of novel solubilizer
  - VI. Nanotechnology

- **Physical Modifications:**
  - I. **Particle size reduction**
    - ✓ Conventional method
    - ✓ Micronization
    - ✓ Nanosuspension
  - II. **Modification of the crystal habit**
    - ✓ Polymorphs
    - ✓ Pseudopolymorphs
  - III. **Complexation**
    - ✓ Physical mixture
    - ✓ Kneading method
    - ✓ Co-precipitate method
  - IV. **Inclusion Complex Formulation Based Techniques**
    - ✓ Kneading method
    - ✓ Lyophilization/ Freeze- drying Technique
    - ✓ Microwave irradiation method
  - V. **Solubilization by surfactants**
    - ✓ Microemulsions
    - ✓ Self microemulsifying drug delivery system
  - VI. **Drug dispersion in carriers**
    - ✓ Solid solutions
    - ✓ Solid dispersions
      - ➢ Fusion Process
      - ➢ Solvent Method
      - ➢ Fusion solvent method
      - ➢ Spray drying
      - ➢ Lyophilization (Spray Freeze Drying Method)
      - ➢ Hot melt Extrusion
      - ➢ Dropping Method
- **pH adjustment**
- **Supercritical fluid process**
- **Liquisolid technique**
- **Polymeric alteration**

- **Chemical Modifications**
  - I. **Salt formation:**

    Salt formation of poorly soluble drug (weak acid and bases) has been a strategy for several decades to enhance solubility. Salts are formed when a compound is ionized in solution. It is an effective method in parenteral and other liquid formulations, as well as in solid dosage forms. The aqueous solubility of an acidic or basic drug as a function of pH dictates whether the compound will form suitable salts [17]. Acidic or basic drug converted into salt having more solubility than respective drug. E.g. Aspirin, Barbiturates. Commercially available example of this approach is Progesterone; a water insoluble steroid which is solubilised in peanut oil [18].
  - II. **Co-crystallization:**

    Co-crystallization alters the molecular interactions and is considered promising alternative to optimize drug properties. A more refined definition of a co-crystal can be "multicomponent crystal that is formed between two compounds that are solids under ambient conditions, where at least one component is an acceptable ion or molecule. Co-

crystals basically consists of two components that are the API and the co-crystal former(s) [19].

**Different techniques for co crystallization**

- ✓ Solvent evaporation
- ✓ Grinding
- ✓ Slurry Co – Crystallization
- ✓ Solvent drop grinding (Modification of Grinding)
- ✓ High throughput co-crystallization
- ✓ Hot melt extrusion
- ✓ Sono crystallization Method [20].

III. **Co-solvency/Solvent Blending:**

The solubility of poorly soluble drugs in water can be increased by mixing it with some water miscible solvent in which the drug is readily soluble. This process is known as co-solvency and the solvent used in combination are known as co solvent. Co solvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly known as solvent blending [21].Poorly soluble compounds which are lipophilic or highly crystalline that have a high solubility in the solvent mixture may be suited to a co-solvent approach. It has found its main use in parentral dosage forms because of low toxicity of many co-solvents, and relatively greater ability of co-solvents to solubilise non-polar drugs. **Commonly used co solvents**:

- ✓ Glycerol, propylene glycol
- ✓ PEG 400
- ✓ Dimethyl Sulfoxide
- ✓ Dimethyl Acetamide
- ✓ Ethanol
- ✓ n-Octanol are the commonly used [22-23].

IV. **Hydrotropy:**

Hydrotropy is a Solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of existing solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water-soluble drugs [24].

**Mixed Hydrotropy:** It is new, simple, cost effective, safe, accurate, precise method which involves the blends of hydrotropes which gives synergistic effect on solubility of poorly water-soluble drug [25].

V. **Use of novel solubilizer:**

The solubility of poorly soluble drug can also be improved by various solubilising materials. Eg, Conventional solubilizer Polysorbates, PEG 400 Sepitrap, Soluplus, Povacoat, dendrimers, is improving the solubility of hydrophobic API [26-27].

VI. **Nanotechnology:**

Nanotechnology is one of the major challenges in drug development is poor water solubility, which leads to bioavailability and reduced therapeutic effects. Around 40-60% of new drug molecules are poorly soluble in water. For many new chemical entities of very low solubility, oral bioavailability enhancement by micronization is not sufficient because micronized product has very low effective surface area for dissolution and next step taken was nanonisation [28].

❖ **Physical Modifications:**

I. **Particle size reduction:**

The solubility of drug is often intrinsically related to drug particle size; as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows greater interaction with the solvent which causes an increase in solubility. Conventional methods of particle size reduction, such as combination and spray drying, rely upon mechanical stress to disaggregate the active compound [29]. The bioavailability of poorly soluble drugs is often related to drug particle size. Increased surface area by reducing particle size improves the dissolution properties and allows a wider range of formulation approaches and delivery technologies. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills and so forth micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug [30-31].

II. **Modification of the crystal habit:**

- ✓ Polymorphs
- ✓ Pseudopolymorphs

Polymorphism is the ability of an element or compound to crystallize in more than one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability. Similarly amorphous form of drug is always more suited than crystalline form due to higher energy associated and increase in surface area. Order for dissolution of different solid forms of drug Amorphous > Metastable polymorph >Stable polymorph.

III. **Complexation:**

Is the association between two or more molecules to form a non-bonded entity with a well-defined stoichiometric [32].

Two types of complex:

- ✓ **Stacking complexes:** It is driven by association of non-polar area of drug and complexes agent this results in exclusion of the non-polar area from contact with water. Stacking can be homogeneous or mixed, but results in clear solution**.**
- ✓ **Inclusion complexes:** It is formed by the inserting the non-polar molecule, region of one molecule into the cavity of another molecule or group of molecules. Cyclodextrin and their derivatives commonly used in complexation.

IV. **Inclusion Complex Formulation Based Techniques:**

Inclusion complexes are formed by the lodging of the non-polar molecule or non-polar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). Commonly used host molecules are Cyclodextrin. The cavity of host must be large enough to accommodate the guest and small enough to eliminate water, Solid inclusion complexes are prepared by various methods such as kneading method co-precipitation, neutralization, co-grinding, spray drying method, and microwave irradiation method [33].

V. **Solubilization by Surfactants:**

Conventional approach to solubilise a poorly soluble substance is to reduce the interfacial tension between the surface of solute and solvent for better wetting and salvation interaction. A wide variety of surfactants like Polyglycolized glyceride, Tweens, Spans, Polyoxyethylenestearates and synthetic block copolymers like Poly (propylene oxide) poly (ethylene oxide)- poly (propylene oxide) like Poloxamers based micelles, Poly(beta-benzyl-L-aspartate)-b-poly(ethyleneoxide), Poly(caprolactone)-b-pol (ethylene oxide) etc

are very successful as excipient and carrier for dissolution enhancement. Improvement of drug solubility by using the amphiphilic surfactants is due to lowering surface tension between drug and solvent, improvement of wetting characteristics and micellar solubilization [34].

VI. **Drug dispersion in carriers**:

**Solid solution** is blend of two crystalline solids that exist as a new crystalline solid. A mixed crystal is formed because the two components crystallize together in a homogenous one-phase system. Hence, it is expected to yield much higher rates of dissolution than simple eutectic systems.

**Amorphous precipitation**: Amorphous precipitation occurs when drug precipitates as an amorphous form in inert carrier [35].

- **pH Adjustment**

Poor water-soluble drug may potentially dissolve in water by applying a pH change To access the solubility by this approach, the buffer capacity and tolerability of the selected pH are important to consider Solubilised excipients that increase environmental pH within the dosage form to a range higher than pKa of weekly acidic drugs increase the solubility of that drug, those excipients that act as alkalizing agents may increase the solubility of weekly basic drugs [36].

- **Superficial Fluid Process**

Supercritical fluids (SCFs) can dissolve non-volatile 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. 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) [37].

- **Liquisolid Methods**

Liquid Compacts are compressible powdered forms of liquid medications. The term “liquisolid medication “implies oily liquid drugs and solutions or suspensions of water insoluble drugs carried in suitable non-volatile solvent systems. Using this technique, a liquid medication may be converted into a dry, non-adherent, free flowing and compressible powder by a simple blending with selected powder excipients such as the carrier and coating material. Surfactants like tweens are used to improve aqueous solubility of poorly soluble drugs [38-39].

- **Polymeric Alteration**

Different crystalline forms of a drug that may have different properties are known as Polymorphs. Polymorphs may differ in physicochemical properties such as physical and chemical stability, shelf-life, melting point, vapor pressure, intrinsic solubility, dissolution rate, morphology, density and biological activities as well as bioavailability [40,41]. Amongst the stable, unstable and metastable crystalline polymorphs, metastable forms are associated with higher energy with increased surface area, subsequently solubility, bioavailability and efficacy [41].

## 5. Conclusion

Dissolution of drug is the rate determining step for oral absorption of the poorly water-soluble drug and the solubility is the basic requirement for the absorption of the drug in GIT. The techniques discussed above are capable of improving the solubility of drug. Selection of method for solubility enhancement depends upon the drug characteristics like physical nature, chemical nature, solubility etc. Suitable selection for solubility enhancement techniques are depends upon characteristics is the key to ensure the goals of good formulation.

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