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A REVIEW: SOLUBILITY ENHANCEMENT TECHNIQUES

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ABSTRACT

Solubility is one of the major parameters to obtain desired concentration of drug in systemic circulation for pharmacological response to be displayed. Poor aqueous solubility of drug molecules remains one of the most critical challenges in pharmaceutical research and development, as it directly affects oral bioavailability and therapeutic efficacy. Nearly 40% of newly developed chemical entities fall into Biopharmaceutical Classification System (BCS) Class II and IV, where dissolution or solubility becomes the rate-limiting step for absorption. To overcome these limitations, a wide range of strategies have been employed, including physical modifications (particle size reduction, nanosuspension, solid dispersion), chemical approaches (salt formation, pH adjustment, co-crystallization, co-solvency) and advanced technological innovations such as nanotechnology, supercritical fluid processing, liquisolid systems and surfactant-based methods. Among these, co-crystallization has gained significant attention for its ability to enhance solubility, dissolution rate, and stability without altering the pharmacological properties of the drug. Additionally, this review highlights the importance of solubility in oral drug delivery, summarizes conventional and novel approaches for improving dissolution, and emphasizes the potential of advanced formulation strategies combined with experimental design tools to overcome challenges associated with poorly water-soluble drugs.

INTRODUCTION

The oral route of drug administration is more preferable, but for many drugs it may be quite challenging and problematic. One of the most important factors is the solubility, mainly aqueous solubility of drug.[1] More than 40% of new chemical entities (NCEs) developed in the pharmaceutical industry are practically water insoluble. These drugs' poor water solubility, combined with their slow absorption, result in insufficient and variable bioavailability, as well as gastrointestinal mucosal toxicity.[2]

Solubility or dissolution enhancement technique is a most challengeable field for the researchers in the formulation design and developmental process of Solubility and the dissolution. These are the main concepts of any physical as well as chemical science including their biopharmaceutical and pharmacokinetic considerations in the treatment with any medicine.[3]

Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, it may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug is represented through various concentration expression such as parts, percentage, molarity, molality, volume fraction, mole fraction.

The Solubility may also be defined as maximum amount of solute that can be dissolved in a given amount of solvent.[4]

The pharmacopoeia lists solubility in terms of number of millilitres of solvent required to dissolve 1 gm of solute. If exact solubilities are not known, the pharmacopoeia provides general terms to describe a given range. These descriptive terms are listed in Table 1.

Table No 01: Expression for approximate solubility.[5]

Descriptive terms	Approximate volume of solvent in millilitres per gram 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 or practically insoluble	More than 10.000

Importance of solubility

The oral ingestion is the most convenient and commonly employed route of drug delivery (easy administration, high patient compliance, cost effectiveness, at least sterility containers and flexibility in the design of dosage form). But, the major challenge with the design of oral dosage forms lies within the poor bioavailability. The cause of low oral bioavailability is due to poor solubility and low permeability.

Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response. Poorly water-soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development. Any drug to be absorbed must be present in the form of an aqueous at the site of absorption.

The poor solubility and low dissolution rate of poorly water-soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. Especially for class II (low solubility and high permeability) substances according to the BCS, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids.

As for BCS class II drugs rate limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility in turn increases the bioavailability for BCS lass II drugs.[6]

Biopharmaceutical classification system:

The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability.[7] BCS system was introduced by the US Food and Drug Administration (FDA)and it classifies the drug into four classes according to permeability and solubility. Solubility impediment is faced in the class II and Class IV of the system facing dissolution as the rate-limiting step for the absorption of a drug due to low solubility.

Table No 02: BCS Classification of drugs.[8]

Class	Solubility	Permeability	Absorption Pattern	Rate limiting step in absorption
I	High	High	Well absorb	Gastric emptying
II	Low	High	Variable	Dissolution
III	High	Low	Variable	Permeability
IV	Low	Low	Poorly absorb	Concentration

Process of solubilisation[9]

The mechanism of solubilization involves breaking inter-ionic / intermolecular bonds of the solute. This separation of the solvent molecule provides space for the solute; which initiates an intermolecular force between the solvent and solute molecule. Solubilization processes are described in below Figure 1

Solubilization process mainly involves 3 steps

Step 1: In solubilization process, a breakdown of solvent bonds takes place and holes can be observed.

Step 2: When the solubilization process occurs intermolecular bonding of the solute (solid) molecules break away due to external kinetic energy.

Step 3: In the presence of external kinetic energy free solute (solid) molecule is integrated in the solvent.

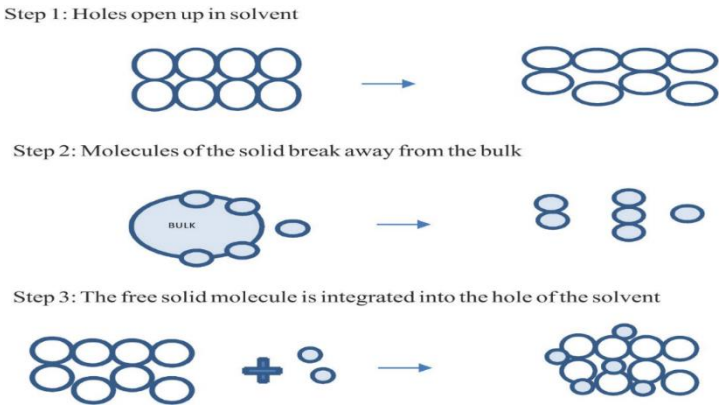

Figure 01: Process of Solubilization.

Factors Affecting solubility

a. **Particle size:** Particle size affects solubility. As particle size decreases, the surface area to volume ratio increases. As the surface area of particle increases it causes greater interaction with solvent. The effect of particle size on solubility can be described.[10]

$$\text{Log}\frac{S}{S_0} = \frac{2\gamma V}{2.303\ R\ T\ r}$$

Where,

S is the solubility of infinitely large particles

S_0 is the solubility of fine particles

V is molar volume

γ is the surface tension of the solid

r is the radius of the fine particle

T absolute temperature in degree Kelvin

R universal gas constant.

b. **molecular size:** The solubility of the substance is decreased when molecules have higher molecular weight and higher molecular size because larger molecules are more difficult to surround with solvent molecules in order to solvate the substance.[11]

c. **Temperature:** The solubility of a solid in a liquid depends on temperature. In the process of solution, if heat is absorbed, the solubility of the solute rises with a temperature rise. In the case of most of the salts. If a solute gives off heat during the process of solution, the solubility of the solute will decrease with an increase in temperature.

d. **Polarity:** The polarity of the solute and solvent molecules will affect the solubility. Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. All molecules also have a type of intermolecular force much weaker than the other forces called London Dispersion forces where the positive nuclei of the atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule.[12]

e. **Pressure:** Solids and liquid solutes have no effect of pressure. But for gaseous solutes increase in pressure increases solubility and decrease in pressure decreases solubility.[13]

f. **Polymorphs:** Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have dissimilar solubility. Generally, the range of solubility changes between different polymorphs is only 2-3fold due to moderately small differences in free energy.[14]

g. **pH**: pH affects the solubility of the compound, the solubility of unionized species is less than that of the ionized solute.[15]

Techniques to overcome poor solubility[16]

I. Physical Modifications

1. Particle size reduction

- Micronization
- Nano-suspension

2. Modification of the crystal habit

- Polymorphs
- Pseudo polymorphs

3. Complexation

- Physical mixture
- Kneading method
- Co-precipitate method

4. Inclusion Complex Formulation Based Techniques

- Kneading method
- Lyophilization/ Freeze- drying Technique
- Microwave irradiation method

5. Solubilization by surfactants

- Microemulsions
- Self-micro emulsifying drug delivery system

6. Drug dispersion in carriers

- Solid solutions
- Solid dispersions

a. Fusion Process
b. Solvent Method
c. Fusion solvent method
d. Spray drying
e. Lyophilization
f. Hot melt Extrusion
g. Dropping Method

II. Chemical modifications

a) Salt Formation
b) pH adjustment
c) Co-crystallization
d) Co-solvency
e) Hydrotropy

f) Use of novel solubilizer

g) Nanotechnology

III. Supercritical fluid process

IV. Liquisolid technique

V. Polymeric alteration

I. Physical modification

1. Particle size reduction

The bioavailability intrinsically related to drug particle size. By reducing particle size, surface area increases which improves the dissolution property of drug. Particle size reduction can be achieved by nanosuspension & Micronization.[17]

a. **Micronization:** Micronization is a process of reducing the size of particles from larger substance to 50 microns in diameter. Micronization increases the solubility by decreasing the surface area. Lower the particle faster the solubility. Micronization technology includes wide range of equipment and process to account for the range of material properties, size shape requirements and other specifications needed for pharma products.[18]

b. **Nanosuspension:** This technique is used to dissolve drugs that are poorly soluble and insoluble in water and oils. Nanosuspension is a biphasic system composed of nanosized particles suspended in water. Surfactants stabilize the nano-sized medication particles for parenteral, pulmonary or oral delivery. The average particle size range in nanosuspension is between 200 and 600 nm and the particle size distribution of solid particles is often less than one micron.[19]

2. Modifications of the crystal habit

Polymorphism 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[20]

3. Complexation

Complexation is the association between two or more molecules to form a nonbonded entity with a well-defined stoichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions.[21]

There are 2 types of complexes they are

a) **Stacking complexes:** Stacking complexes are formed by the overlap of the planar regions of aromatic molecules. Nonpolar moieties tend to be squeezed out of water by the strong hydrogen bonding interactions of water. This causes 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. Stacked complexes can be homogeneous or mixed.

b) **Inclusion complexes**: Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The major structural requirement for inclusion complexation is a snug fit of the guest into the cavity of host molecule. The cavity of host must be large enough to accommodate the guest and small enough to eliminate water, so that the total contact between the water and the nonpolar regions of the host and the guest is reduced.[22]

4. Solubilization by surfactants

Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitter-ionic or non-ionic. When small apolar molecules are added they can accumulate in the hydrophobic core of the micelles. This process of solubilization is very important in industrial and biological processes. The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent. Mainly 2 methods.[23]

a) **Microemulsion**: Microemulsions are a promising drug technique used to enhance the bioavailability, solubility, and therapeutic efficacy of hydrophilic drugs. They can improve drug delivery by incorporating hydrophilic drugs within a thermodynamically

stable and transparent oil-in-water emulsion. This can optimize the drug's solubility and permeability, leading to enhanced bioavailability and therapeutic efficacy.[24]

b) **Self-Micro emulsifying drug delivery Systems**: Self-emulsifying systems use the concept of in situ formation of emulsion in the gastrointestinal tract. The mixture of oil, surfactant, co-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).[25]

5. Drug dispersion in carriers

a) **Solid solutions**: A solid solution comprising a poorly water-soluble drug or a solid solvent having solid solute dissolved in it which have good water solubility are comparable to the liquid solution, Solid solutions are resultant single phase, which come into being when two compounds disperse in each other at their molecular level. Both the compounds then crystallize out simultaneously leading to formation of homogenous single-phase system.[26]

b) **Solid dispersion**: Solid dispersions (SDs) are defined as the dispersion of one or more active ingredients in an inert carrier or matrix in the solid-state. SDs are viewed as single-phase mixtures of an active ingredient and water-soluble polymers that are believed to provide improved aqueous dissolution and oral bioavailability. The SDs can be used to improve the bioavailability of poorly water-soluble drugs with different physicochemical properties since they allow the gastrointestinal (GI) concentrations to be increased by increasing their apparent solubility and rate of dissolution.[27]

Different methods in Solid Dispersion[28]

- Fusion process
- Melting method
- Solvent method
- Melting solvent method (melt evaporation)
- Melt extrusion methods
- Lyophilization techniques
- Melt agglomeration Process
- The use of surfactant

II. Chemical modification

a) **Salt formation:** Salt formation is the most preferred approach to enhance aqueous solubility of pure drug, some of the API cannot be formulated in its pure form due to various issues of instability, thus they are converted to solid forms such as salts, co-crystals, solvates, hydrates, and polymorphs. Each of them imparts a different physiochemical property and affects performance characteristics stability, bioavailability, purification and manufacturability of the drug in their better way.[29]

b) **pH Adjustment**: Poor water-soluble drug may potentially dissolve in water by applying a pH change. To access the solubility of this approach, the buffer capacity and tolerability of the selected pH are important to consider. Solubilized 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.[30]

c) **Co-solvency:** 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. The cosolvents are having hydrogen acceptor or donor groups with a small hydrocarbon region. 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 ensure water solubility. Some of the co-solvents used in this system are glycerine, propylene glycol, dimethyl sulfoxide, ethanol and N,N dimethylformamide and PEG 300.[31]

d) **Hydro trophy**: Hydro trophy is a Solubilization technique in which a large amount of a second solute is added, increasing the solubility of the first solute in water. It improves solubility more directly through a process known as complexation, which involves weak interactions between hydrotropic substances such as sodium benzoate, sodium acetate, sodium alginate, urea and drugs that are poorly soluble. Hydrotropic agents are ionic organic salts. Many salts with large anions or cations that are also very soluble in water, a phenomenon known as "hydrotropism," cause the "salting in" of non-electrolytes known as "hydrotropic salts." A weak contact exists between the hydrotropic agent and the solute in hydrotropic solutions, which are non-colloid.[32]

e) **Nanotechnology:** Nanotechnology broadly refers to the study and application of materials and structures at the nanoscale level, typically around 100 nanometres (nm) or

less. Due to the extremely small effective surface area of micronized products, Micronization alone is often insufficient to enhance the oral bioavailability of many new chemical entities with very low solubility. As a result, Nanonization emerged as the next step in improving drug solubility and absorption. Various preparatory techniques, such as high-pressure homogenization, vacuum deposition, high-temperature evaporation, and milling, can be employed to achieve Nanonization.

f) **Co-Crystallization:** Cocrystallization is an advanced technique used to enhance the physiological, chemical, and physical properties of an active pharmaceutical ingredient (API). By forming a stable crystalline structure between the API and a suitable co-crystal former, this approach improves solubility, stability, and bioavailability. Unlike solvates, which involve a liquid and a solid component, co-crystals are composed entirely of solid constituents. The selection of an optimal co-crystal is guided by rational physicochemical research and analytical methods, making it a crucial strategy in pharmaceutical development.[33]

METHODS OF PREPARATION OF CO-CRYSTALS

Co-crystals can be prepared by solvent and solid based methods. Common methods used in preparation of co-crystals are given as below.

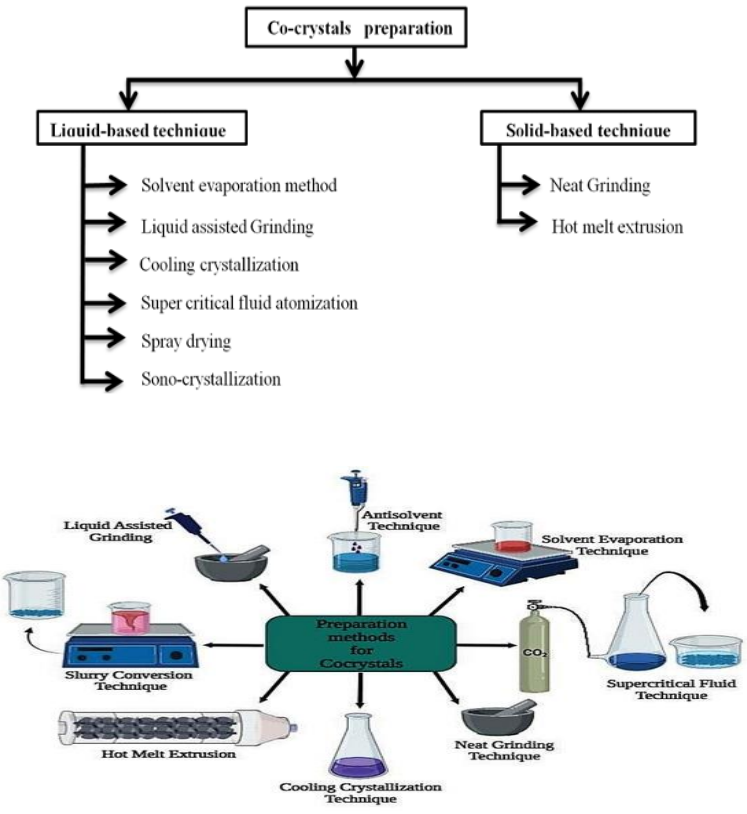

Figure 04: Various techniques involved in preparation of co-crystals.[41]

Solid-BASED METHODS

1. Neat Grinding (Dry grinding)

Dry grinding is a cocrystallization method without a solvent. The solid materials that will result in the cocrystal are admixed in appropriate stoichiometric amounts, pressed and crushed together with a mortar and pestle or a ball mill or vibrator mill. The common grinding duration ranges from 30to60min.with this method, numerous cocrystals can be prepared and any failure is generally due to the use of inappropriate settings. Reducing the particle size increases the specific surface area of interaction between the materials for the development of intermolecular bonds. This offers the advantage of increased selectivity compared to cocrystallization through dissolution.[42]

2. wet grinding

This is a modification of neat grinding method.it includes mixing the two components and adding a very small amount of solvent (for example a few tenths of an equivalent of solvent per mole of the component) during the grinding process resulting in a significantly higher kinetics of cocrystal formation. In this process solvent act as a catalyst, either as media that facilitate molecular diffusion or as an important factor that forms multicomponent inclusion framework and has been used enhance supramolecular selectivity in crystalline systems. The effect of the solvent can be described as catalytic as its small amount is not part of the final product.[43]

SOLUTION-BASED METHODS

1. Anti-solvent method

Heat-sensitive compounds benefit from anti-solvent crystallization, which uses less heat energy than a solvent evaporation method and can be carried out at temperatures close to those found in the atmosphere. The difficulty in separation of solvents from the mixture limits its reuse.

2. Sonocrystallization method

Ultrasound aided cocrystallization or Sono crystallization is another liquid assisted technology that has been employed for the synthesis of nanocrystals. In this technique during and coformers are dissolved in an appropriate vehicle (solvent). Cold water passes throughout the sonication process to take care of the constant temperature of the sonicator and forestall fragmentation. The energy that is imparted to the sample during irradiation causes a rapid rise in temperature in a short period of time, which leads to melting of crystalline material

followed by material mixing and then rapid recrystallization upon cooling. One proposed condition for the conformer material which can be used for this method is that the conformer must be in sublimable condition in order to support a nucleation process through the vapour phase.

3. Solvent evaporation method

This approach involves dissolving the API and conformer in a common solvent at the proper stoichiometric ratio. To produce co-crystals the solvent was then allowed to gradually evaporate at room temperature. When choosing a solvent, it is essential to take API and coformers solubilities into account. The quality of the co-crystal is significantly influenced by the solvent present during co-crystal formation. According to the theory behind this method, the functional division of pharmaceuticals and a complimentary conformer engage in intermolecular interactions such hydrogen bonding and make products that are thermodynamically advantageous. This methods drawback is that it doesn't work well on a broad scale.[47]

4. Cooling crystallization method

The drug gets recrystallized by supersaturating the solution at a different temperature. At 40.0 ± 0.5^0c an adequate amount of drug was dissolved in a certain solvent volume. In a water bath, the solution was cooled to 10.0 ± 0.5^0c while being stirred continuously at a cooling rate about 0.25^0c/min. crystals were collected by vacuum filtration. cleaned three times in distilled water, allowed to dry for 24hrs at room temperature and then stored in a desiccator.[44]

5. Supercritical fluid atomization technique

Rapid expansion of supercritical solutions (RESS)is a process where solution of the drug and conformer in supercritical co2 are rapidly depressurized(10-5s) to atmospheric conditions. CO-Crystallization with super critical solvent (CSS) technique uses the solvent power of supercritical CO_2 to suspend the API and conformer as the slurry in liquid or supercritical co_2. Due to fluids drastic decrease in solvent power, the solvent in the depressurized supercritical co_2 is highly supersaturated. When a super saturation forms quickly it triggers nucleation and crystallization which drives the fine particles to participate. The process employs non-toxic, extremely volatile solvents that don't leave any solvent residues on the crystals that are created. The limited solubility of the drug-coformer pairings in supercritical co_2 and the low product yields are some drawbacks of RESS.

APPLICATION OF PHARMACEUTICAL CO-CRYSTALS

Cocrystal engineering is relevant to the production of energetic materials, pharmaceuticals, and other compounds. Of these, the most widely studied and used application is in drug development and more specifically, the formation, design, and implementation of active pharmaceutical ingredients, or API's. Changing the structure and composition of the API can greatly influence the bioavailability of a drug. The engineering of cocrystals takes advantage of the specific properties of each component to make the most favorable conditions for solubility that could ultimately enhance the bioavailability of the drug. The principal idea is to develop superior physicochemical properties of the API while holding the properties of the drug molecule itself constant.[45]

CONCLUSION

Enhancing the solubility of poorly water-soluble drugs continues to be a major focus in pharmaceutical research, as solubility directly governs dissolution, absorption, and ultimately bioavailability. Oral drug delivery, though the most preferred route due to its convenience and patient compliance, often faces challenges when active pharmaceutical ingredients exhibit poor aqueous solubility. Addressing this issue is essential for ensuring therapeutic effectiveness and clinical success.

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