Methods to boost solubility

[1]Vaishnavi Bhaskar Borgaonkar, [2]Achal Harinarayan Yelane

[1]Research scholar, [2]Research scholar
Department of Pharmaceutics
P.R. Pote Patil College of Pharmacy, Amravati, India

***Abstract*- The process of a solid dissolving in a liquid phase to create a homogenous mixture is known as solubility. A crucial factor in getting the right quantity of drug into the bloodstream to show a pharmacological effect is solubility. Low water solubility of the novel therapeutic compound is the main issue with formulation. Poorly aqueous soluble medications need substantial dosages to reach their maximum therapeutic plasma concentration after oral delivery. Using the biopharmaceutical classification system (BCS), substances are categorized according to their solubility and permeability. Regulatory agencies and health organizations have adopted this categorization system to enable dissolution to be used to verify bioequivalence for highly soluble and highly permeable chemicals. Drugs with poor water solubility dissolve slowly, which reduces their bioavailability when taken orally. This review article aims to increase bioavailability and promote efficient absorption.**

***key words*- solubility, permeability, bioavailability, biopharmaceutical classification system, absorption.**

I.INTRODUCTION

Solubility refers to the greatest quantity of solute that may be dissolved in a certain quantity of solvent. It may be characterized both mathematically and qualitatively. Quantitatively, it is precisely defined as the solute's concentration in a saturated solution at a certain temperature. Solubility may be described as the natural interaction between two or more compounds to create a uniform molecular mixture [1]. Significant challenges faced by several pharmaceutical firms include low water solubility and limited bioavailability [2]. Pharmaceutical compounds that possess high solubility have favorable absorption when taken orally, leading to enhanced bioavailability. The most critical stage in the development of drugs, especially for oral medications, is the improvement of drug solubility [3]. Solubility is an essential characteristic that impacts the capacity of the active pharmaceutical ingredient (API) to dissolve and be absorbed by the body, thereby influencing its effectiveness and the required dose [4].

Enhancing the solubility of drugs, and therefore their oral bioavailability, is a very complex task in the drug development process, particularly for oral drug delivery systems. There are several methods documented in literature to improve the solubility of drugs that have low water solubility. The selection of procedures is based on specific factors like the characteristics of the medicine being considered, the qualities of the excipients to be chosen, and the type of the planned dosage form. Orally given medications achieve full absorption only when they have sufficient solubility in the stomach and exhibit excellent bioavailability [5]. The drug's solubility is a crucial factor to be considered during the production of pharmaceutical goods. The low solubility of medicines in water reduces their bioavailability. Various methods may be used to improve the solubility or dissolution of drugs.

1. A medicine is considered poorly soluble if its aqueous solubility is less than 100 ug/ml.
2. Poor dissolution: < 0.1 mg/cm 2/min for intrinsic dissolution rate.
3. Molecular weight greater than 500.
4. A high energy crystal.

The Biopharmaceutics Classification System (BCS), developed by the US Food and Drug Administration (FDA), categories pharmaceuticals into four classes according on their solubility and permeability characteristics. Low solubility causes a soluble obstacle in Classes II and IV of the system, where dissolution is the rate-limiting step for drug absorption.

Drugs with low water solubility—that is, BCS Class II or even Class IV compounds—present issues with absorption related to dissolution.

Table 1 BCS Classification

Sr .no	BCS Class	Solubility	Permeability	Example
1.	Class I	High	High	Metoprolol Amlodipine
2.	Class II	Low	High	Ibuprofen Naproxen

3.	Class III	High	Low	Cimetidine Ranitidine
4.	Class IV	Low	Low	Furosemide Nelfinavir

II.Factors affecting solubility

- Particle size
- Temperature
- Molecular size
- Nature of solute and solvent
- Pressure
- Polarity
- polymorphs
- pH

- **Particle size**

Particle size can, in fact, significantly affect a substance's solubility. In comparison to larger particles of the same substance, smaller particles have a larger surface area. There are more places for the solvent and solute to come into contact thanks to the increased surface area.

- **Temperature**

Temperature has an impact on the ability of a substance to dissolve. If the solution process absorbs energy, the solubility will increase as the temperature rises. When energy is liberated during the process of dissolving, the solubility of the substance will diminish as the temperature increases.

- **Molecular size**

The solubility of a material is diminished by bigger molecules with higher molecular weight and size, since it becomes more challenging to solvate these molecules by enveloping them with solvent molecules.

- **Nature of solute and solvent**

The nature of the solute and solvent is determined by the concentration of the solute in a certain quantity of solvent at a particular temperature. As an example, the solubility of lead (II) chloride at room temperature is limited to 1 gramme per 100 grammes of water, but zinc chloride may dissolve up to 200 grammes in the same amount of water.

- **Pressure**

In the case of gaseous solutes, solubility the value rises as the pressure increases and falls as the pressure drops. Variations in pressure have no bearing on the solubility of liquid or solid solutes.

- **Polarity**

The solubility of a substance is determined by the relative polarity of the molecules in both the solvent and the solute. Typically, polar solute molecules will dissolve in polar solvents, while non-polar solute molecules will dissolve in non-polar solvents.

- **Polymorphs**

Polymorphism is the property of a material to undergo crystallization in several unique crystalline forms. A polymorphic agent has the ability to undergo crystallization in several different forms. A solid may undergo the process of crystallization and give rise to several forms or polymorphs. Polymorphs may have different melting points. The solubility of polymorphs is influenced by the relationship between their solubility and melting point.

III.METHODS

TECHNIQUES FOR SOLUBILITY ENHANCEMENT

Multiple methods exist for enhancing the solubility of hydrophobic pharmaceutical compounds. Several conventional and innovative methods to enhance solubility include

NEW TECHNIQUES TO OVERCOME POOR SOLUBILITY

1. Chemical Modifications:
   1) Salt Formation

2) Co-crystallization
3) Co-solvency
4) Hydrotropic
5) Use of novel solubilizer

2. Physical Modifications:
1) Particle size reduction
a) Micronization
b) Nanosuspension
2) Modification of the crystal habit
a) Polymorph
3) Inclusion Complex Formulation Based
a) Kneading method

1. Chemical modification

The chemical alteration of is at the forefront of advancements in biological imaging and biopharmaceutics.

1) Salt formation

The process of salt production is widely recognised as the most prevalent and efficient approach to enhance the solubility and dissolution rates of both acidic and basic pharmaceutical compounds. Multiple variables, including S0 (intrinsic solubility), pH, pKa, Ksp (solubility product), and pH max (pH of maximum solubility), contribute to the overall outcome [6].

Salts are produced by the process of ionization of a chemical in a solution. This approach is efficacious in parenteral and other liquid formulations, as well as in solid dosage forms.

An acidic or basic medicine is transformed into a salt form that exhibits higher solubility compared to the original drug. Examples include Aspirin, Theophylline, and Barbiturates. An example of this strategy that is available for purchase is Progesterone, which is a steroid that is not soluble in water but can be dissolved in peanut oil [7].

2) co-crystallization

Co-crystallization modifies the molecular interactions and is seen as a possible approach for enhancing medicinal characteristics. A co-crystal may be defined as a multicomponent crystal that forms between two solid substances under ambient circumstances, with at least one component being an acceptable ion or molecule. Co-crystallization mitigates the numerous physical, chemical, or physiological limitations of an active pharmaceutical ingredient (API). The co-solvency mechanism enhances the solubility of a non-polar solute by reducing the tension at the interface. An optimal co-crystal may be chosen using analytical methodologies and sensible physicochemical examinations, including assessments of solubility and stability. The only distinction between solvates and cocrystals is in the physical condition of their constituents. If one of the constituents is in a liquid state while the other is in a solid state, it is referred to as solvates. Conversely, if both constituents are in a solid state, they are referred to as cocrystals. Pharmaceutical Co-crystals are composed of two main components: the active pharmaceutical ingredient (API) and the cocrystal formation [7].

Different techniques for co crystallization

a) Solvent evaporation
b) Grinding
c) Slurry Co – Crystallization
d) Solvent drop grinding (Modification of Grinding)
e) Hot melt extrusion
f) Sono crystallization Method

3) Co-solvency/ Solvent Blending

The most prevalent method for enhancing the solubility of pharmaceuticals in water is by cosolvency, which involves blending a safe and non-toxic organic solvent with water.

To enhance the solubility of a pharmaceutical that is not easily soluble in water, one may add a water-miscible solvent in which the drug has high solubility. This is performed by reducing the tension between the aqueous solution and the hydrophobic medication. The pharmaceutical formulation maintains a steady liquid condition. The co-solvent approach is appropriate for poorly soluble compounds that are lipophilic or highly crystalline and have a high solubility in the mixture of solvents. The main use of this substance is in injectable drug formulations because of the low toxicity of some co-solvents and their excellent ability to dissolve nonpolar medications. The often-used cosolvents are glycerol, propylene glycol, PEG 400, dimethyl sulfoxide, dimethyl acetamide, ethanol, and n-octanol [7].

4) Hydrotropy

Hydrotropes are a heterogeneous group of compounds that were first described by Neuberg about a century ago. These substances have an amphiphilic molecular structure and possess the capacity to significantly enhance the solubility of organic molecules that are not very soluble in water [7].

Hydrotropy is a unique and unparalleled method of increasing the solubility of poorly soluble substances using specific chemical components called hydrotropes. This approach may significantly enhance solubility under normal circumstances. The enhanced solubility in water is likely attributed to the creation of structured aggregates of hydrotrope molecules at a certain concentration. Hydrotropes are a kind of molecule that are both soluble in water and have the ability to reduce the surface tension of liquids. They have the capacity to greatly increase the solubility of organic solutes, including acids, esters, alcohols, aldehydes, ketones, hydrocarbons, and lipids. Hydrotropes have extensive uses in medicine solubilization, detergent formulation, health care, home applications, and as extraction agents for fragrances [8].

5) Use of novel solubilizer

Various solubilizing agents may enhance the solubility of poorly soluble drugs. For instance, the solubility of hydrophobic active pharmaceutical ingredients (APIs) may be enhanced by using conventional solubilizers such as Polysorbates, PEG 400 Sepitrap, Soluplus, Povacoat, and dendrimers.

II. Physical Modifications

1) **Particle size reduction**

The solubility of a medicine is often inherently linked to the size of its particles. As the size of particles decreases, the ratio of surface area to volume rises. A greater surface area facilitates enhanced contact with the solvent, resulting in an elevation in solubility. The bioavailability of medications with low solubility is often associated with the size of drug particles. Reducing particle size enhances dissolving characteristics and expands the possibilities for formulation techniques and delivery systems by increasing surface area [7].

a) Micronization

The use of medication powders comprising micronized drug particles has been on the rise in various pharmaceutical dosage forms to address challenges related to dissolution and bioavailability. The majority of recently created medications have low water solubility, which restricts their capacity to dissolve quickly and be absorbed by the body. Micronizing the medication particles might increase the solubility rate. The characteristics of the micronized drug material, including particle size, size distribution, shape, surface properties, agglomeration behavior, and powder flow, are influenced by the specific micronization technology used. Mechanical commination, spray drying, and supercritical fluid (SCF) technologies are the most often applied procedures for creation of micronized medication particles however the features of the final therapeutic product cannot be regulated using these techniques [9]. The digestive absorption of poorly soluble medicines is contingent upon their dissolving rate. Reducing the particle size of these medications enhances their dissolving rate [10].

b) Nanosuspension

The inherent features of nanosuspension, including its ease of modification, process flexibility, targeting capabilities, and changed pharmacokinetic profile leading to safety and effectiveness, have made it an effective and promising approach for delivering insoluble medicines [11]. A nanosuspension is a dispersion that contains just the weakly water-soluble medication, with no additional matrix material. The process of preparing nanosuspensions is straightforward and can be used for any medications that are not soluble in water. A nanosuspension effectively addresses the challenges of low solubility and bioavailability, while also modifying the drug's pharmacokinetics to enhance both safety and effectiveness [12]. Nanosuspension systems were established based on several parameters, such as the amplitude and duration of ultrasonication. [13].

2) **Modification of the crystal habit**

Crystallization advancements have successfully attained control over the identification and purity of drugs, but control over the physical structure remains inadequate. This paper examines the impact of solvents used in the crystallization process on the shape and clumping together of crystals, which may have implications for their dissolution. Scientific literature has shown that modifying the habits of crystals using appropriate solvents may improve their ability to dissolve by altering the size, quantity, and characteristics of the crystal faces that come into contact with the dissolving substance. The enhanced dissolution rate of the medication from the agglomerates of crystals, as compared to the single crystals, may be attributed to the porous nature of the agglomerates, which results in improved wettability [14].

a) Polymorph

Polymorphs, which include anhydrous and solvate/hydrate forms, have the potential to address these issues with drug absorption. However, maintaining their physicochemical stability during the whole shelf life of the medication may be challenging. Moreover, the alteration of the polymorphic structure has often resulted in clinical setbacks upon its release in the market [15]. Polymorphism is a frequent occurrence in pharmaceuticals, where it may negatively impact their quality by altering their physical and chemical characteristics, including solubility, and thus decreasing their bioavailability. Polymorphism is the phenomenon where a substance may exist in several crystal structures. Polymorphs are substances that have the same chemical makeup but vary in the arrangement of their molecules in the crystalline form (Bilton et al., 1999; Karpinski, 2006; Desiraju, 2008; Purohit et al., 2009) [16].

3. Inclusion Complex Formulation Based

a) Kneading method

Kneading rapidly combines high-performance materials (HPs) with a solution of polyethyleneimine (PEI) polymer, resulting in the generation of a "dough" that aids in the creation of stable suspensions in water-based solutions [17]. The ultimate dimensions may be adjusted based on the quantity and characteristics of the salt-kneading substance. The presence of this technique enables pharmaceutical researchers to use a size-reduction procedure that produces minuscule, spherical, and easily flowing particles of the poorly soluble active pharmaceutical ingredient (API), while also minimizing the occurrence of undesirable needle-like shapes [18]. In order to optimize the kneading process, the quantity of solvent and mixing time was used as independent variables, and the super disintegrants were utilized to create the appropriate formulation [19]. Pharmaceutical powders were kneaded when wet using different blade components and operation circumstances. The compressive characteristics of a wet kneaded mass were examined, and the distribution of a hindering liquid (water) throughout the mass was explored by analyzing a tracer aqueous pigment [20].

IV.CONCLUSION

In conclusion, various solubility enhancement techniques play a pivotal role in improving the bioavailability of poorly soluble drugs. Approaches such as Salt Formation, Co-crystallization, Co-solvency, Hydrotropy, use of novel solubilizer also Micronization, Nanosuspension, Polymorph, kneading method have demonstrated efficacy in overcoming solubility challenges. By addressing these limitations, these techniques contribute to the development of more effective and accessible pharmaceutical formulations, ultimately advancing drug delivery and therapeutic outcomes.

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