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Techniques for Improving Solubility

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Abstract
The goal of this review is to look into numerous aspects that could improve the solubility and bioavailability of drugs that aren't particularly water soluble. The oral route of administration is the most popular and widely accepted form of delivery for many drugs due to its simplicity of intake. Medication with slow dissolving rates indicate partial absorption, resulting in restricted bioavailability when administered orally. Particle size reduction, micronization, cosolvency, hydrotropy, pH adjustment, sonocrystallization, supercritical antisolvent technique, solid dispersion, inclusion complexation, micro emulsion, and liquid solid methods have all been used to improve the solubility of drugs that are poorly soluble in water. This review's authors discussed a variety of ways for boosting drug absorption and bioavailability, as well as a variety of solubility improvement patents.

Keywords: *Solubility, Solubility enhancement, Bioavailability, Novel methods*

I. Introduction

Solubility refers to the greatest amount of solute that can dissolve in a given amount of solvent. A quantitative as well as a qualitative definition are both possible. It is quantified as the solute concentration in a saturated solution at a certain temperature. A qualitative definition of solubility is the spontaneous interaction of two or more substances to produce a homogenous molecular dispersion. A solution is considered to be saturated when the solute and solvent are in equilibrium. To depict a drug's solubility, many concentration expressions such as parts, percentages, molarity, molality, volume fractions, and mole fractions are utilized [1, 2, 3]. A variety of strategies can be used to increase the solubility of hydrophobic medicines. If substances may pass through the epithelium orally, the fraction of orally absorbed medicine may rise because the poorly soluble drug's solubility increases as compared to water alone. pH alteration is frequently combined with co-solvents to improve the solubility of a poorly soluble medication. If the precipitate after dilution is fine or amorphous, bioavailability can be improved due to a wider concentration gradient and higher surface area for dissolution. When the medicine precipitates into poorly soluble particles that must be dissolved slowly, the bioavailability may be inadequately increased. This method is often used in surveys to evaluate the efficiency of poorly soluble drugs due to its universality and relative simplicity. However, if the poorly soluble medication precipitates uncontrollably after coming into contact with a pH level (oral or parenteral) where the drug is substantially less

soluble, the data interpretation may be inaccurate. Some traditional and cutting-edge strategies for increasing solubility are as follows:

II. IMPORTANCE OF SOLUBILITY

Oral intake is the most practical and widely utilized mode of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, lack of sterility limitations, and flexibility in the formulation of dosage forms. As a result, many generic drug manufacturers are more likely to develop bioequivalent oral medicine formulations [4]. The poor bioavailability of oral dose forms, on the other hand, is the most serious design issue. Some of the characteristics that influence oral bioavailability are aqueous solubility, drug permeability, dissolving rate, first-pass metabolism, presystemic metabolism, and sensitivity to efflux mechanisms. The two most common causes of low oral bioavailability are poor solubility and insufficient permeability. Other dosage forms, such as parenteral formulations, rely largely on solubility as well [5]. One of the crucial factors in attaining the needed drug concentration in the systemic circulation for the desired pharmacological reaction is solubility [6]. Poorly water-soluble medicines may require high dosages after oral delivery to achieve therapeutic plasma concentrations. Low water solubility is the fundamental difficulty in generating formulations for new chemical entities as well as generics. Any medicine that is to be absorbed must be present in the form of an aqueous solution at the absorption site. Water is the chosen solvent for liquid pharmaceutical formulations. Most drugs are poorly soluble in water and are either weakly basic or moderately acidic. Over 40% of novel chemical entities (NCEs) developed by the pharmaceutical industry are fundamentally water insoluble. The slow drug absorption of these weakly water-soluble drugs results in insufficient and variable bioavailability, as well as harm to the gastrointestinal mucosa. Solubility is the most important rate limiting factor for drugs taken orally because it permits the drug to reach the desired concentration in the systemic circulation for pharmacological response. The solubility problem is a serious challenge for formulation scientists. [7]. One of the most difficult aspects of medication development, particularly for oral-drug delivery systems, is increasing drug solubility and, as a result, oral bioavailability. There are various methods documented in the literature for increasing the solubility of poorly water-soluble compounds. The procedures are selected depending on a variety of parameters, including the properties of the drug under consideration, the type of excipients to be used, and the type of dosage form desired. Inadequate bioavailability is usually caused by poorly water-soluble medicines' weak solubility and sluggish rate of dissolution in aqueous gastrointestinal fluids. Increases in the solubility and rate of dissolution of the medicine in gastrointestinal fluids, especially for class II (low solubility and high permeability) drugs, may improve bioavailability. Because solubility in stomach fluid and drug release from the dosage form are the rate-limiting processes for BCS class II drugs rather than absorption, increasing solubility boosts BCS class II pharmacological bioavailability [4, 7, 8].

III. TECHNIQUE FOR IMPROVING SOLUBILITY

Formulation procedures are required early in the drug discovery process when compound solubility in aqueous media is minimal, and they remain critical for the selection of the lead material and the development of commercial medicinal products. [16]. Poorly water-soluble drugs have been engineered to dissolve and dissolve faster in a variety of ways, including the ones listed below:

1) Particle Size Reduction
2) Micronization
3) Cosolvency
4) Hydrotropy
5) pH Adjustment
6) Sonocrystallization
7) Supercritical Antisolvent technique
8) Solid Dispersion
9) Inclusion Complexation
10) Micro Emulsion

11) Liquisolid Methods

1. PARTICLE SIZE REDUCTION

Because a particle's surface area to volume ratio increases as it grows smaller, drug solubility is typically inversely associated with particle size. The bigger surface area allows for greater interaction with the solvent, enhancing solubility [9]. Mechanical stress disaggregates the active component in conventional particle size reduction procedures such as comminution and spray drying. The industry is well-versed in the critical comminutional factors that allow for successful, reproducible, and cost-effective particle size reduction. However, the physical stress exerted to the medicinal product during comminution operations such as milling and grinding may cause deterioration. Thermal stress that may occur during comminution and spray drying is also a concern when processing thermosensitive or unstable active compounds. Furthermore, standard procedures typically fail to reduce the particle size of essentially insoluble (0.1 mg/mL) medications [10,11,12].

2. MICRONIZATION

Micronization is another frequent approach for lowering particle size. Micronization increases drug surface area, which speeds up dissolution but does not increase equilibrium solubility [13]. The rate of dissolution of these drugs is increased by decreasing the particle size, which results in an increase in surface area. Milling technologies such as jet mills, rotor stator colloid mills, and so on are used to micronize drugs. Micronization is not ideal for pharmaceuticals with large dosage numbers since it does not change the drug's saturation solubility. Fenofibrate, diosmin, progesterone, spironolactone, and griseofulvin were employed in these procedures. Each drug was micronized to improve gastrointestinal absorption and thereby bioavailability and therapeutic effectiveness [14,15].

3. COSOLVENCY

Co-solvency/Solvent Blending: This technique reduces the interfacial tension between the aqueous solution and the hydrophobic solute, hence increasing the solubility of a drug that is poorly soluble in water. Liquid pharmaceuticals are always sold. Poorly soluble compounds that are lipophilic or highly crystalline and have a high solubility in the solvent mixture may benefit from a co-solvent method. Because of the low toxicity of many co-solvents and their relative superior ability to solubilize nonpolar medicines, it has found major use in parenteral dosage forms. Glycerol, propylene glycol, PEG 400, dimethyl sulfoxide, dimethyl acetamide, ethanol, and n-octanol are common cosolvents [16, 17].

4. HYDROTROPHY

Another solvent is used in the solubilization process known as hydrotropy to boost the solubility of the mixtures. The addition of numerous additives can improve an additive's water solubility. Despite the fact that the process used in the works is in non-micelle-forming materials, whichever solids or solids, whether inorganic or organic, are capable of solubilizing insoluble compounds, its mechanism is solubility because it is related to Complexation, which involves the weak interaction between the hydrotropic agents [9]. In the following approach, hydrotropy is split into three categories: aromatic catatonics, aromatic anionics, and linear anionics. Examples include sodium acetate, sodium alginate, and other hydrotropy agents. The benefits of this technique are that it suggests a superior solubilizing method and that the solvent is independent of the PH. Additionally, a wide range of compounds have been reported to display hydrotropic conditions [18, 19].

5. pH- ADJUSTMENT

Ionic medications that are more easily soluble require PH to be soluble. The pH of a medication is the most important factor influencing its solubility and pharmacological effect. PH is required for the administration of medications. Because blood has an acidic content that affects it, a drug with a low solubility can precipitate rather than be soluble in it. The optimum PH should be required for drug absorption. The degree of solubility permits chemicals to enter the body. The stomach has a PH of 1-2, while the duodenum has a PH of 5-6. This approach is commonly used in pre-clinical studies to adjust pH. It is a novel method for determining how well low-soluble medications operate. The advantage of this procedure is that it is simple to formulate the

formulation and uses a minimal amount for evaluation [20].

6. SONOCRYSTALLIZATION

Sonocrystallization is a revolutionary particle engineering approach that promotes the solubility and dissolution of hydrophobic pharmaceuticals while also investigating its impact on the crystal properties of the drug. To minimize particle size, ultrasound-assisted recrystallization of insoluble materials using antisolvents and liquid solvents has also been successful. To cause crystallisation, sonocrystallization employs ultrasonic energy with a frequency range of 20-100 kHz. The majority of applications employ ultrasonic frequencies ranging from 20 kHz to 5 MHz. Melt sonocrystallization (MSC) is a promising sonocrystallization technology for obtaining porous, amorphous materials with high stability [21].

7. SUPERCRITICAL ANTISOLVENT TECHNIQUE

This approach was first used in the late 1980s. Since Hannoy et altests .'s in 1879, numerous methods for supercritical fluid-assisted particle design have been developed and patented. Carbon dioxide is used in the supercritical fluid antisolvent method not as an antisolvent for the solute but as the solvent of an organic solvent. Because of its low critical temperature and pressure, supercritical carbon dioxide is useful for processing heat-labile pharmaceuticals. When the procedure is completed, it is non-toxic, non-flammable, inexpensive, and much easier to remove from polymeric materials. Even when a little amount of carbon dioxide remains trapped inside the polymer, the client is not at risk. Supercritical particle production methods are a novel and effective method for increasing pharmaceutically active chemical bioavailability [22].

8. SOLID DISPERSION

In the early 1960s, Sekiguchi and Obi investigated the manufacture and efficacy of eutectic melts of a sulfonamide medicine and a water-soluble carrier and proposed the concept of solid dispersions. 8 Solid dispersions are a useful pharmaceutical method for improving medicine absorption, therapeutic efficacy, and dissolution in dosage forms. Solid dispersion is a collection of solid products that contain at least two distinct components, typically a hydrophilic matrix and a hydrophobic medicine. For solid dispersions, the hydrophilic carriers Plasdone-S630, Polyvinylpyrrolidone, and Polyethylene Glycols are most commonly used. Surfactants are commonly employed in the manufacture of solid dispersion. Surfactants include Tween-80, Docusate sodium, Myrj-52, Pluronic-F68, and Sodium Lauryl Sulphate. Celecoxib9, halofantrine solubility [23], ritonavir [24] can be improved by using adequate hydrophilic carriers in solid dispersion.

9. INCLUSION COMPLEXATION

The inclusion complex formation technique has been employed more precisely than any other solubility enhancement method to boost the aqueous solubility, dissolving rate, and bioavailability of poorly water-soluble medications. Inclusion complexes are formed when a nonpolar molecule or nonpolar portion of one molecule (referred to as the guest) is inserted into the cavity of another molecule or group of molecules (known as host). The key structural requirement for inclusion complexation is that the guest molecule fits firmly into the cavity of the host molecule. To limit total contact between water and the nonpolar regions of the host and the guest, the cavity of the host must be large enough to accommodate the guest while still being small enough to drain away water. The following approaches are used to prepare for the formation of inclusion complexes of poorly soluble medicines in order to improve their water solubility. [25].

10. MICRO-EMULSION

The micro-emulsion method can be used to dissolve medicines with low solubility. It can act in conjunction with the injection of a protein mixture into the body to boost the solubility of some drugs that are nearly insoluble in aqueous form. A hydrophilic surfactant, an oil-water mixture, and a pure pre-concentrate are all components of a micro-emulsion that can easily dissolve a drug that is soluble in it [26]. When the preparations come into contact with water, they quickly dissolve, forming a translucent emulsion of tiny, homogeneous oil droplets containing the solubilized drug. This approach is isotropic, thermodynamically stable, and employs

clean water, oil, and surfactant systems. It is usually employed in conjunction with a co-surfactant, and the size range of its droplets is (20–200 nm). All low viscosity fluids can be made in homogeneous systems using a wide variety of surfactant concentrations in both water and oil. The fundamental disadvantage of micro-emulsions is that they have greater co-surfactant/surfactant concentrations, making them unsuitable for intravenous delivery. The drug precipitates when its micelle concentration falls below a particular threshold and surfactant microemulsions are diluted; nonetheless, absorption is still increased due to the precipitate's microscopic particle size. The advantage of micro-emulsions is that they are simple to prepare and include a soluble drug with the highest bioavailability. [27, 28].

11. LIQUISOLID METHODS

When a medicine dissolved in a liquid vehicle is put into a carrier material with a porous surface and fibers in its interior, such as cellulose, both absorption and adsorption occur. Specifically, the liquid is initially absorbed in the interior of the particles and captured by its internal structure, and once saturated, the liquid adsorbs onto the internal and external surfaces of the porous carrier particles. By having high adsorptive capabilities and a large specific surface area, the coating material then imparts the necessary flow characteristics to the liquid-solid combination. As coating materials, crystalline and amorphous silica and cellulose powders can be used. [29].

IV. CONCLUSION

The solubility phenomenon, which is the dissolution of a solid in a liquid phase to produce a homogeneous molecular dispersion, is critical to the success of a drug. The majority of the active pharmaceutical components, on the other hand, are hydrophobic and poorly soluble in water. One of the most difficult formulation development challenges is the drug's solubility. Due to insufficient water solubility, important chemicals are unable to reach the final drugs, preventing them from reaching their full therapeutic potential. As a result, despite their potential pharmacokinetic activity, the limited water solubility of many innovative drugs is a major impediment to their successful market release. If a molecule's bioavailability is limited by its solubility in water, it is impossible to create compounds that have a significantly beneficial effect on their physiological target. The drug's aqueous solubility also influences its physical and chemical properties, dosage, gastrointestinal stability, rate of solid dissolution, rate and extent of absorption, and achievement of the desired drug concentration in the systemic circulation for the desired (anticipated) pharmacological response. As a result, solubility is an important concept in the development of drugs.

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