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Review Article

A Promising Approach of Solid Dispersion for Enhancement of Solubility

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ABSTRACT

The preferred technique to increase the solubility of several medicines has been solid dispersion. Using the appropriate medium or polymer in conjunction with the solid dispersion of one or more active pharmaceutical ingredients in a carrier at a solid state is necessary to improve the dissolution of some low water-soluble medications and thus increase their bioavailability. It has attracted a lot of attention as a way to quicken up the disintegration rate. It occurs as a result of dispersing some water-soluble carriers with some weakly water-soluble medications to improve the pharmaceuticals' disintegration. The solubility performance of pharmaceuticals is one of the most challenging areas of dosage form formulation and development. The amount of weakly water-soluble chemicals has significantly grown, prompting extra care to make them more soluble. The manufacture of solid dispersions must take into account a few factors, such as the choice of carrier and physicochemical characterization techniques. A brief overview of solid dispersion, including its characteristics, benefits, drawbacks, and uses in different formulations, is provided in this review article.

INTRODUCTION

Because of their low levels of absorption, medications with limited water solubility frequently have poor oral bioavailability. Drugs with low absorption by dissolution can have their rate of dissolution increased by size reduction or micronization, although this causes the particles to aggregate and becomes less wettable. Other methods for boosting the bioavailability of pharmaceuticals that are poorly soluble in water include complexation with cyclodextrin, solubilization with a co-solvent, salt creation, and particle size reduction; however, each of these methods has its own set of drawbacks. By creating solid dispersions of weakly bioavailable medications, the shortcomings of earlier methods were overcome [1].

Solubility and Its Types

The ability of a chemical substance, known as a solute, to dissolve in a solid, liquid, or gaseous solvent and create a homogenous solution in the solvent is known as solubility. A substance's solubility is mostly dependent on the solvent employed, temperature, and pressure. The saturation concentration, or the point at which adding more solute does not increase its concentration in the solution, is used to quantify the degree of solubility of a material in a certain solvent [2].

Absolute/Intrinsic Solubility

Absolute or intrinsic solubility is the highest quantity of solute dissolved in a given solvent under unfavourable pH, pressure, and temperature conditions. It's a fixed attribute.

Saturated Solubility

The most solute that can be dissolved in a particular solvent until it reaches saturation. Additional solute will not dissolve in solvent Table 1.

Importance of Solubility

Due to its ease of administration, high patient compliance, cost effectiveness, lack of sterility constraints, and flexibility in dosage form design, oral ingestion is the most practical and widely used method of drug delivery. Consequently, a large number of generic medicine manufacturers are more likely to create oral bioequivalent pharmaceutical products.

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Table 1: USP and BP Solubility Criteria.

Descriptive term	Part of 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 1000
Practically insoluble	10000 and over

Nonetheless, the main challenge in the development of oral dose formulations is their low bioavailability. Aqueous solubility, drug permeability, dissolving rate, first-pass metabolism, pre-systemic metabolism, and sensitivity to efflux mechanisms are some of the variables that affect oral bioavailability. Low permeability and poor solubility are the most common causes of low oral bioavailability. Another important factor in various dosage forms, such as parenteral formulations, is solubility. One of the key factors in reaching the appropriate drug concentration in the systemic circulation and the necessary pharmacological response is solubility. When taken orally, poorly soluble medicines may need substantial dosages to achieve therapeutic plasma concentrations. The primary issue with the formulation development of novel chemical entities and the production of generic drugs is low water solubility. At the site of absorption, any medication that is to be absorbed needs to be there as an aqueous solution. When it comes to liquid medicinal formulations, water is the preferred solvent. The majority of medications have limited aqueous solubility and are either weakly basic or mildly acidic. Over 40% of NCEs (New Chemical Entities) created in the pharmaceutical sector are essentially water insoluble. These slowly absorbed, weakly water soluble medications cause gastrointestinal mucosal damage as well as insufficient and inconsistent bioavailability. The most crucial factor limiting the rate at which oral medications can reach the appropriate concentration in the systemic circulation for pharmacological action is their solubility. One of the biggest challenges facing formulation scientists is the solubility problem. Enhancing a medication's solubility and, consequently, its oral bioavailability continues to be one of the most difficult parts of the drug development process, particularly for oral drug delivery systems. To improve the solubility of medications that are poorly soluble in water, varieties of methods are available and have been documented in the literature. The approaches are selected based on a number of factors, including the drug's qualities, the type of excipients to be used, and the type of dosage form that will be used. Insufficient bioavailability is frequently caused by poorly water-soluble medicines' weak solubility and slow rate of dissolution in aqueous gastrointestinal fluids. Increasing the drug's solubility and dissolution rate in the gastrointestinal fluids can improve its bioavailability, particularly for compounds classified as class II (high permeability and low solubility) by the BCS. Since drug release from the dosage form and solubility in the stomach fluid—rather than absorption—are the rate-limiting steps for BCS class II medicines, enhancing solubility also raises the drugs' bioavailability [3-4].

Solid Dispersion

One of the most effective methods for increasing the release of poorly soluble medicines is the use of solid dispersions. In 1961, solid dispersions were first explained by Sekiguchi and Obi. One of the key tactics for addressing the oral absorption of poorly soluble substances that is limited by dissolution rate is solid dispersion. Particle size reduction, enhanced wetting, decreased agglomeration, changeability in the drug molecules' physical state, and potentially a disperse at the molecular level in accordance with the physical state of the solid dispersion are all possible outcomes of formulating poorly soluble compounds as solid dispersions. A collection of solid goods made up of at least two distinct components—typically a hydrophilic matrix and a hydrophobic drug—are referred to as solid dispersions. There will be an amorphous or crystalline matrix. The medications will be dispensed molecularly in either crystalline or amorphous particles (clusters) [5].

Types of Solid Dispersion

1. **Eutectic Mixtures:** In order to create physical blends of extremely translucent crystals of two compounds, eutectic mixtures of solids are typically created by rapidly cooling common components [6].

2. **Solid Solution:** Two components crystallise together in an inhomogeneous one-phase system, known as a solid solution. The drug's particle size is reduced to molecule size in solid solution. As a result, in contrast to

matching eutectic mixtures, a solid solution can achieve a quick dissolving rate [7-8].

3. **Discontinuous Solid Solutions**: Each component's solubility is restricted to that of another component in a discontinuous solid solution. A typical phase diagram displays the region of a genuine solution. In some areas, one component completely dissolves into other solid components. Below a particular temperature, two components that are interchangeably soluble begin to dissolve.

There are two types of solid dispersion based on the way according to the solvate molecules are distributed in the solvendum. These are as:

a. **Substitutional crystalline solutions**: In this kind of solution, solute molecules take the place of solvent molecules (in the solid solvent's crystal lattice). Using this method, both continuous and discontinuous solutions can be constructed. According to their potential sizes, the solvent and solute have comparable proportions**.**

b. **Interstitial crystalline solid solutions** In the interstitial solid solution, the dissolved molecule is found in the spaces between the crystal lattice. A discontinuous solid state is formed by it. Less than 20% of the volume should consist of solute molecules.

c. **Amorphous Solid Solutions**: the amorphous solid dispersion of solute molecules at the molecular level, but with an uneven arrangement inside the amorphous solvent. The drug precipitates in an amorphous form; otherwise, this procedure is the same as the eutectic mixture. The scientists Chiou and Rieglman were the first to report the creation of an amorphous solid dispersion, which improved the drug's dissolving capabilities [9-12].

4. **Glass Solutions and Glass Suspensions**: When a solute dissolves in a glassy solvent, it describes a homogenous glassy system. One of two substances—a pure chemical or a mixture of chemicals in a glassy translucent state—is referred to as glass. By quenching the melt, the substance can return to its glassy or translucent form. This is described as brittleness and clarity below the glass transition temperature. A glass solid solution that has a single phase contains multi-ingredient glassy systems. At the molecular level, it is uniform and homogeneous. In this system, the dissolved molecules are distributed molecularly, and the carrier typically exists in an amorphous state [13-14].

Advantages of Solid Dispersion [15-17]:

- Reduction in particle size: different carrier use in solid dispersion reduces particle size of drug particle which improve solubility and bioavailability.
- Improve wettability of particle: solid dispersion improves wettability of particle.
- Improve porosity: Solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore, result in a higher dissolution rate.
- Improve dissolution which ultimately improves the solubility and bioavailability.

Disadvantages of Solid Dispersion [17, 18]:

- The undefined condition of medication may experience crystalline state, in this way poor soundness is the issue of strong scattering.
- Handling issue show up because of thickness of some strong scatterings.
- In nearness of dampness and extraordinary temperature strong scattering might be disintegrated, that can result in precious stone development.
- Shelf life forecast of indistinct material is troublesome.
- Hygroscopicity of polymers utilized in strong scattering retains dampness that can result in change of nebulous structure into crystalline form.
- The instability is the major disadvantage of the solid dispersion. The deteriorating effect on solid dispersions such as moisture and temperature have more on physical mixture because of tackiness it is difficult for east handling of solid dispersion.

Mechanism of Enhanced Dissolution in Solid Dispersion

There are several elements that can either raise or decrease the solid dispersion's dissolving rate. Among these are the following factors:

1. **Reduced Particle size or Reduced Agglomeration:** Both have to do with the drug's exposed surface area increasing and particle size decreasing. Size reduction has been attributed to the creation of solid or eutectic solutions. It has also been proposed that the presentation of particles to the dissolving solvent as physically distinct entities could lessen aggregation. Many of the carriers used for solid dispersion may have some wetting capabilities, which could reduce agglomeration and enhance surface area through better wetting.

2. **Increased solubility or Dissolution rate of the drug:** By utilising several carriers, the drug's solubility could rise. As a result, the release of the medication was governed by the carrier rather than the characteristics of the medication. Second, certain systems exhibit release behaviour that is more reliant on the drug's characteristics than the polymer.

3. **From crystalline to amorphous state transformation/ Formation of high Energy State:** Drugs that are amorphous have minimum stability, a higher energy state, and can be thought of as cooled liquids. They have a higher water solubility than crystalline forms because transferring a molecule from a crystal requires more energy than it does for non-crystalline (amorphous) solids. For instance, novobiocin is ten times more soluble in its amorphous form than in its crystalline form.

4. **Wetting:** When a liquid and a solid have a high affinity for one another, the liquid covers the solid's surface in a film. There is an angle of contact between the liquid and the solid when this affinity is weak or nonexistent, making it harder for the liquid to dispense the air. Three interfacial forces are in balance, resulting in this contact angle [19-21].

Method of Preparation [22-27]

1. **Fusion Method**:
   The fusion process was utilised to make the initial solid dispersions intended for use in medicinal applications. Only in cases where the initial materials are in their crystalline state is it referred to as the melt process. At temperatures higher than their eutectic temperature, a drug and carrier mixture with a eutectic composition melts. The molten material is then ground into a powder after solidifying on an ice bath.
2. **Freeze-drying Method:**
   Using this procedure, the medication and carrier are dissolved in a common solvent and then submerged in liquid nitrogen until completely frozen. The frozen solution is then lyophilized once again. One major benefit of freeze drying is that during the solid dispersion generation process, the medication experiences very little heat stress. Additionally, as soon as the solution is vitrified, the possibility of phase separation is reduced.

3. **Spray-drying:**
   With this technique, the medication and carrier are dissolved or suspended, and the solvent is then sprayed into a heated air stream to evaporate. Owing to the droplets' huge specific surface area, the solvent evaporates quickly, forming the solid dispersion in a matter of seconds—possibly quickly enough to avoid phase separation.

4. **Dropping Method:**
   This is a novel process that turns melted solid dispersions into spherical particles. Since this technique doesn't employ organic solvents, it is free from the issues related to solvent evaporation.

5. **Solvent Evaporation Method:**
   The medication and carrier are dissolved in a volatile solvent (such as ethanol, chloroform, or a combination of ethanol and dichloromethane) and then the solvent is evaporated. This process is known as the solvent evaporation method. For the regulated rate and low temperature solvent removal, vacuum evaporation can be employed. By using freeze-drying, the solvent can be removed more quickly. Utilising an azeotropic solvent mixture in water can help get over the challenges associated with choosing a common solvent for both the medication and the carrier.

6. **Co-precipitation Method**:
   This approach involves gradually adding non-solvent to the medication and carrier solution while continuously stirring. During the non-solvent addition process, the medication and carrier co-precipitate to create microparticles. The final step is to

filter and dry the microparticle suspension that was produced.

7. **Hot Melt Extrusion Method:**
   An extruder is used in this procedure to combine the components very thoroughly. The barrel, hopper, heating jacket, kneading screw, and die are the parts of the extruder. The medication and carrier are physically mixed, put into the hopper, run through a screw, and then extruded from the die. This process yields a product that can be handled with ease because it can take on any shape.

8. **Supercritical Fluid Methods:**
   Supercritical fluid methods are mostly applied with carbon dioxide (CO_2), which is used as either a solvent for drug and matrix or as an anti-solvent. When supercritical CO_2 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of organic solvents and since CO_2 is considered environmentally friendly, this technique is referred to as 'solvent free'. The technique is known as Rapid Expansion of Supercritical Solution (RESS).

Application of Solid Dispersion:

- It is mainly applicable in obtaining homogeneous distribution of a small amount of drug in solid state.
- It helps to stabilize the unstable drug
- It is used to dispense both the liquid or gaseous compound in a solid dosage state.
- The fast release primary dose can be formulated in a sustained dosage form.
- It is also used to formulate sustained release of soluble drug by using poorly soluble or insoluble carrier.
- By polymorph is given in solid dispersion system such as solid solution, eutectic mixture [28].

CONCLUSION

One of the most efficient ways to improve the solubility and bioavailability of drugs that are not very soluble in water is through solid dispersion. Therefore, it is necessary to resolve a few issues pertaining to the drug's stability and flow characteristics. Thus, the best and most alternative option for increasing the solubility of the weakly water soluble BCS-II medication is a solid dispersion with a synthetic or natural carrier that is less toxic, biocompatible, and more readily available. the improvement of oral bioavailability and release rate of poorly water-soluble medications through the use of solid dispersion and cautious carrier selection. Delaying or slowing down the drug's release pattern is also possible.

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