SOLID DISPERSION – A TECHNOLOGY FOR SOLUBILITY ENHANCEMENT OF POORLY SOLUBLE DRUGS

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Abstrac*t:*

Solubility plays a crucial role in the effectiveness of orally administered pharmaceutical drugs, particularly those with poor water solubility. A significant Abstract: Solubility plays a crucial role in the effectiveness of orally administered pharmaceutical drugs, particularly those with poor water solubility. A significant proportion of newly developed drug candidates fall into Biopharmaceutical Classification System (BCS) classes II and IV, characterized by low solubility and/or permeability, which impedes their bioavailability. To address these limitations, several formulation strategies have been devised, with solid dispersion emerging as a widely adopted and effective technique. Solid dispersions involve the molecular dispersion of poorly soluble drugs into hydrophilic carriers, enhancing dissolution rates and bioavailability. This review provides a comprehensive overview of solid dispersion, a solubility enhancement technique, with a detailed focus on the classification, preparation methods, mechanisms and evaluation of solid dispersions. Additionally, it explores the evolution of solid dispersions across four generations and highlights their pharmaceutical applications, paving the way for improved therapeutic outcomes and formulation development.

Keywords: *Bioavailability, Dissolution, Hydrophilic carriers, Solid dispersion, Solubility enhancement*

1. INTRODUCTION

The ability of a chemical substance known as a solute to dissolve in a solid, liquid or gaseous solvent and create a homogenous solution of the solute in the solvent is known as solubility. Temperature, pressure and the solvent employed all have a basic impact on a substance's solubility. The saturation concentration, wherein adding more solute does not increase its concentration in the solution, is a measure of a substance's degree of solubility in a particular solvent [1]. Oral medications are mostly based on their permeability and solubility. Poor permeability and water solubility are the most prevalent conditions that limit drug absorption from the gastrointestinal tract. High dosages are necessary for these medications to enter the bloodstream. Oral routes are difficult for researchers to design and improve because of their poor solubility, permeability and substantial first pass effect. A common issue with medication candidates in today's pharmaceutical research pipeline is their poor water solubility. It is commonly stated that between 75 and 90 percent of drug items in development and 40 percent of marketed pharmaceuticals have poor water solubility. Poorly soluble medications are removed from the gastrointestinal tract (GIT) before they dissolve, which lowers their bioavailability and diminishes their therapeutic benefits [2]. A medication must be released from the dosage form and dissolved in the gastrointestinal fluids before it can be absorbed when taken orally in a solid dosage form, such as a tablet, capsule or solution. Many weakly water-soluble medications have restricted bioavailability due to their dissolution rates, which are regulated by the surface area they are present for dissolution [3]. Class II and Class IV pharmaceuticals of the Biopharmaceutics Classification System (BCS) are medications with low solubility [4]. The BCS categorization is based on publicly available data. Sixty-one of the 130 oral medications on the WHO list could be categorised with accuracy Class I includes about 34% of the categorized drugs (highly soluble, highly permeable), followed by Class II with 37% (poorly soluble, highly permeable), Class III with 22% (highly soluble, poorly permeable), and Class IV with 7% (poorly soluble, poorly permeable). The absorption rate and extent of Class II and IV drugs are strongly influenced by solubility and permeability, which in turn affect their bioavailability. Therefore, increasing the solubility of BCS Class II and IV drugs can significantly enhance their bioavailability.[5]The Biopharmaceutical Classification System which divides drugs into four classifications based on solubility and permeability are given in table 1.

Table 1: Biopharmaceutical Classification System

Class	Solubility	Permeability	Absorption pattern
I	High	High	Well absorbed
II	Low	High	Variable
III	High	Low	Variable
IV	Low	Low	Poorly absorbed

Importance of Solubility

Drugs that are poorly soluble will dissolve slowly, which will reduce their bioavailability when taken orally.Bioavailability is the extent and speed at which a medicines active ingredient enters the bloodstream and enables the drug to reach the site of action. A medication with inadequate bioavailability will have little therapeutic potential and provide undesirable clinical outcomes. To reach therapeutic medication concentrations in the blood, dose escalation may be necessary in some situation. This could lead to toxicity in the gastrointestinal tract and decrease patient adherence to treatment. Most novel medications are challenging to formulate into drug delivery systems because of their limited water solubility. Because of this, improving the solubility of process for developing pharmaceutical products.[6]

Methods to Enhance Solubility: [7]

Various techniques have been used to improve solubility and dissolution rates of poorly water soluble drugs which include as following:

a) Particle Size Reduction

b) Nanonization

c) Cosolvency

d) Hydrotropy

e) pH Adjustment

f) Sonocrystallization

g) Supercritical Fluid (SCF) Process

h) Solid Dispersion

i) Inclusion Complexation

j) Self-Emulsifying or Self-Micro Emulsifying Systems

k) Liquisolid Methods

Solid Dispersion:

Sekiguchi and Obi created a workable technique in 1961 that allows for the removal of many of the aforementioned restrictions on the bioavailability augmentation of poorly water-soluble medications. This technique was subsequently known as solid dispersion [8]. One of the best methods for enhancing the release of poorly soluble medications is the use of solid dispersions. These are molecular combinations of weakly water-soluble medications in hydrophilic carriers that have a drug release profile influenced by the characteristics of the polymer. The majority of current studies on solid dispersion systems have focused on their use in the creation of extended-release dosage forms, in addition to increasing bioavailability. However, it is challenging to adapt the systems to solid dispersion dosage forms because to a number of reasons, including a complex preparation process, low repeatability of physicochemical properties, challenges in developing and scaling up formulations and physical instability for solid dispersion. Re-crystallization of the medication must be avoided during its release from the dosage form, particularly to maintain a supersaturation level for a prolonged period of time.[9]

Classification Of Solid Dispersion:

In their initial classification of solid dispersions, Chiou and Riegelman divided them into six categories: amorphous precipitations in a crystalline carrier, compound or complex formation, solid solutions, glass solutions and glass suspensions, simple eutectic mixtures and combinations of the first five categories. For a long time, this classification was often used and recognized. Nonetheless, a number of changes to the classification scheme have been suggested recently. Three generations of solid dispersions have been distinguished in the recent evolution of solid dispersion method. Control release solid dispersion (CRSD) was added as the fourth generation and this classification was further altered. Even though these evaluations offer valuable categorization schemes for solid dispersions, further work is required to develop a precise classification scheme and link it to the stability and solubility of solid dispersions.[10]

I. Classification Based On Molecular Arrangement:

1. Eutectic Mixtures
2. Solid Solutions
    - Substitutional solid solutions
    - Interstitial solid solutions
    - Continuous solid solutions
    - Discontinuous solid solutions

3 . Amorphous Precipitations

1. Eutectic Mixtures:

Eutectic mixtures are frequently made by rapidly cooling the melt of the two components to produce a physical mixture of incredibly thin crystals of the two components. In order to create a physical mixture of extremely thin crystals of the two components, solid eutectic mixtures are typically created by quickly cooling the co-melt of the two components.

2. Solid Solutions:

The two elements crystallize together to form a homogenous, one-phase system in a solid solution. In the solid solution, the drug's particle size is lowered to that of its molecules. Therefore, a solid solution can dissolve more quickly than a similar eutectic mixture. There are two ways to categorize solid answers. The two components can be categorized as continuous or discontinuous based on how miscible they are. The two substances are miscible in all quantities in continuous solid solutions. [11]

a. Substitutional solid solutions:

This kind of solid solution only occurs when the solute molecule sizes differ from the solvent particles by less than 15%. [12]

b. Interstitial solid solutions:

The soluble particles in interstitial solid solutions occupy the spaces between the solvent molecules in the crystal lattice. As a result, the diameter of the solute molecule should be smaller than 0.59 times that of the solvent molecule. [13]

c. Continuous solid solutions:

Both components are completely miscible with one another in a solid solution. The continuous solid solution's constituents should have a stronger connection than either of the individual components. Although it is theoretically feasible, there isn't any solid pharmaceutical research to support this claim. [14]

d. Discontinuous solid solutions:

Each component's solubility in the other component is restricted in the case of discontinuous solid solutions. For practical reasons, Goldberg et al., have proposed that the phrase "solid solution" should only be used when the two components mutual solubility surpasses. [15]

3. Amorphous Precipitations:

In contrast to a eutectic mixture, where the drug and the carrier crystallize out at the same time, a drug may precipitate out in an amorphous form in the crystalline carrier in this situation. A drug's amorphous form dissolves more quickly than its crystalline form. Since little energy is required to break the crystal lattice during the dissolving

process, Taylor and Zografi claim that utilizing the medication in its amorphous state can typically improve drug release [16]

II. Classification Based On Generations:

On the basis of the composition and preparation of solid dispersions, it can be categorized into four generations.

First Generation Solid Dispersion:

First, the term "solid dispersions" was coined in a study by Sekiguchi and Obi, in which a eutectic combination was created that enhanced the oral bioavailability and dissolving rate of water-insoluble medications. These solid dispersions, which were made with crystalline carriers such as urea, sugars and organic acids, were dubbed as first generation solid dispersions. However, these initial solid dispersions were linked to the development of crystalline solid dispersions, which were thermodynamically stable but lacked the ability to accelerate drug release as compared to amorphous dispersions. [17]

Second Generation Solid Dispersion:

Amorphous carriers took the place of crystalline ones in the second generation of solid dispersions. In this case, the medication is molecularly distributed within an amorphous polymeric medium. These carriers, which are further classified into synthetic and natural product-based polymers, were widely employed for solid dispersions because they could create amorphous solid dispersions. Polyethylene glycol, povidone and polymethacrylates are examples of synthetic polymers. Natural polymers are made of various cellulose derivatives such as hydroxypropyl cellulose or ethylcellulose or derivatives of starch such as cyclodextrines. [18]

Third Generation Solid Dispersion:

A surfactant carrier or a combination of amorphous polymers and surfactants serve as carriers in these solid dispersions. For medications with low solubility, these provide the maximum level of bioavailability. Inulin and poloxamer 407 are the surfactants utilized in the third-generation solid dispersion. [19]

Fourth Generation Solid Dispersion:

Poorly water-soluble medications with short biological half-lives were used in the fourth generation solid dispersion, commonly referred to as controlled release solid dispersion (CRSD). Enhancing solubility and achieving regulated prolonged release are its two goals. In this generation, the solubility of the drug will be improved by its molecular dispersion in a carrier, but the release of the medication may be delayed by the use of water-swellable polymers. This allows us to administer a sufficient amount of medication for a longer duration, which has several advantages, including a longer

therapeutic effect for medications with short biological half-lives and poor water solubility, fewer side effects and a reduced frequency of dosing, which increases patient compliance.The polymers which are used include ethyl cellulose, hydroxypropyl cellulose, Eudragit RS, RL, poly (ethylene oxide) and carboxyvinyl polymer. [20] Materials used as carriers are given in table 2.

Table 2: Materials Used as Carriers in Solid Dispersion

Materials Used as Carriers	Examples
Sugars	Sorbitol, Mannitol
Acids	Citric acid,Succinic acid
Polymers	Poly Vinyl Pyrollidones (PVP, PVP K-30, PVP K-90), Poly Ethylene Glycol (PEG-400, PEG-6000)
Insoluble polymer or Enteric polymer	HPMC phthalate, Eudragit(L-100,S-100,RL,RS)
Surfactants	Tweens,Spans
Surfactant Polymer	Poloxomer 188, Gelucire 44/14, Lutrol F-127, Soluplus
Miscellaneous	Urea

Mechanism Of Solid Dispersion:

Polymers are carriers in solid dispersions. When a drug and polymer come into close contact, the drug fills the gaps in the polymeric chain, giving it some flexibility. For instance, in the hot melt extrusion technique, the polymer is heated to a point where the heat causes the polymer chain to relax and the drug molecule to be incorporated into it. In contrast, the solvent utilized in the spray drying process is what causes the weak cohesive intra- and intermolecular connections of the polymer chain, which leads to the creation of solvent-polymer interactions. The drug molecules that have been dissolved in the solvent are then integrated into the polymer chains that have been loosened. If a substance becomes stiff and brittle when another component is added, this is known as the Antiplasticization effect. The compound with the low glass transition temperature(Tg) of the resultant mixture would fall midway between the Tgs of the two compounds, to put it another way. In this instance, the medication experiences Antiplasticization. However, as the polymer's Tg drops, it plasticizes. [21]

Preparation Methods Of Solid Dispersion:[22]

1. Melting Method
2. Solvent Evaporation Method
3. Lyophilization Technique
4. Hot Melt Extrusion Method
5. Spray Drying
6. Electrospinning
7. Super Critical Fluid (SCF) Technology
8. Kneading Method

1. Melting Method:

Here, the medication and carrier are properly combined using a mortar and pestle to create a uniform dispersion and the combination is heated above the drug's and carrier's melting points. After cooling, a solid mass is formed, which is subsequently crushed and sieved to produce dispersion. However, this approach has a number of disadvantages because it is irrelevant for thermolabile medications and high-melting-point polymers like PVP. [23]

2. Solvent Evaporation Method:

This procedure involves dissolving the mixture, including the medication and carrier, in a common solvent, which is then evaporated until a free film remains. [24] The mixture is then dried and sieved. The two main variables that impact the solid mass are the type of solvent and the temperature at which the solvent evaporates. The performance of the product is significantly impacted by minor changes in the solvent evaporation conditions used in both techniques. Since the majority of organic solvents are linked to toxicity problems, even the organic solvent that was utilized should be appropriately eliminated.[25]

3. Lyophilization Techniques:

Heat and mass are transferred to and from the product being prepared during the freeze-drying process. This approach was put out as a substitute for solvent evaporation. In order to create a lyophilized molecular dispersion, the drug and carrier are co-dissolved in a shared solvent, frozen and then sublimed [26]. This process is known as lyophilization. The benefits of freeze drying include minimizing the possibility of phase separation as soon as the solution is vitrified and exposing the medicine to very little heat stress throughout the solid dispersion process.[27]

4 . Hot Melt Extrusion Method:

Solid dispersions with the binder serving as a carrier have been made in this method. Further more, solid dispersions are made by either heating the binder, drug and excipients to a temperature higher than the binder's melting point (a process known as "melt-in") or using a high shear mixer to spray a drug dispersion in molten binder onto the heated excipients (a process known as "spray-on"). [28]

5. Spray Drying:

The required quantity of carrier is dissolved in water and the medication is dissolved in the proper solvent. After combining the solutions using sonication or another suitable method, a clear solution is produced, which is then spray-dried with a spray dryer. In the formulation process known as "spray-drying," a hot gas stream atomizes, sprays and dries an excipient mixture (typically a polymer dispersion containing a medication) in a chamber. [29]

6. ElectroSpinning:

A polymeric fluid stream solution or melt that is supplied through a millimeter-scale nozzle is used in the electrospinning process to create solid fibers. A conducting capillary attached to a reservoir holding a polymeric solution and a conductive collective screen was subjected to an electric field during this procedure. This method has been used to make Itraconazole HPMC solid dispersion.[30]

7. Super Critical Fluid (SCF) Technology:

This approach uses carbon dioxide as a solvent for the organic solvent but as an anti-solvent for the solute. Using a nozzle that uses carbon dioxide, the medication and carrier are dissolved in a shared solvent to create a particle forming vessel. [31] Additionally, the process can be completed at room temperature by taking use of carbon dioxide's capacity to plasticize and swell polymers. Additionally, by lowering the melting temperature of the dispersed active ingredient, supercritical fluids are employed to lower the temperature of the melt dispersion process. The relatively mild temperature range of 35 to 75°C used in this procedure enables the handling of heat-sensitive biomolecules, including proteins and enzymes.This technique lowers particle size and residual solvent content without causing any deterioration. [32]

8. Kneading Method:

This process turns the carrier into paste by allowing water to seep through it. After that, the drug is added and kneaded for a specific amount of time. After being kneaded, the mixture is dried and, if required, sieved. [33]

EVALUATION PARAMETERS OF SOLID DISPERSION:

Percentage Yield:

The percentage practical yield is calculated to know about the efficiency of the solid dispersion preparation method, which helps in the selection of a suitable method of production. Solid dispersions were collected and weighed to determine practical yield from the following equation .[34]

$$\textit{Practical Yield (\%)} = \textit{(Practical yield)/(Theoretical yield)} \times 100$$

Phase Solubility Study:

In this study, an excessive amount of medication is introduced to a carrier aqueous solution in certain dissolving media with rising carrier concentrations. The flask is then sealed and shaken in a water bath with a thermostat set to 37°C. Following filtering, the filtrate is appropriately diluted and subjected to spectrophotometric analysis at an appropriate wavelength. [35]

Saturation Solubility Study:

Batches of drugs and solid dispersions are added in excess to 25 milliliters of distilled water until it reaches super saturation. After that, it is kept at 37 °C ± 0.5°C for 48 hours in an orbital flask shaker. After passing through Whatman-filter paper, it is examined using a UV spectrophotometer to determine the drug's concentration. [36]

Drug Content:

To determine the drug content, a known amount of solid dispersion is dissolved in a solvent and subsequently examined using a UV spectrophotometer. The following formula is used to determine the percentage of drug entrapment efficiency. [37]

% Entrapment efficiency =(Actual drug content)/(Theoretical drug content) × 100

***In vitro* Release Study:**

In vitro dissolution testing is an essential part of evaluating solid dispersions because it provides tangible evidence of the improvement in the medication's rate and extent of dissolution when compared to the pure drug and its physical combination. The dissolution research often uses standard USP dissolution equipment, such as Apparatus I (basket type) or Apparatus II (paddle type). A suitable dissolution medium, usually a buffer pH 6.8 phosphate buffer or 0.1N HCl, is selected based on the drug's solubility characteristics. The paddle or basket is rotated at a set speed, usually between 50 and 100

rpm and the temperature is maintained at 37 ± 0.5°C to mimic physiological circumstances. Samples are removed, filtered and analyzed using UV-visible spectrophotometry or high-performance liquid chromatography at predetermined intervals. The cumulative proportion of medicine released is calculated and displayed in order to compare the release profile of the solid dispersion with that of the pure medication. [38].

Characterization of Solid Dispersion:

Fourier Transform Infrared Spectroscopy (FT-IR):

The main application of FT-IR is in drug-polymer (carrier) compatibility studies. Its primary use is to investigate how drugs and polymers interact in solid states.[39]

Differential Scanning Calorimetry (DSC):

It is an effective method for researching amorphous material. Additionally, it can identify exothermic and endothermic peaks. On the basis of melting point, it also investigates whether or not the medicine was integrated into the polymer (carrier). [40]

Powder X-ray Diffraction (PXRD):

It is mostly useful for to characterize whether the solid dispersion is amorphous or crystalline in nature in Sharper peak indicate more crystallinity.

Scanning Electron Microscopy (SEM):

It is used for to characterize particle morphology. The surface morphology of the layered sample was examined using SEM. The small amount of powder was carefully applied to a double-sided carbon tab and carbon-coated tape that was attached to stubs of metal. These sample stubs were coated with a thin layer (30Å) of gold using the POLARON-E 3000 sputter coater and images were captured at various magnifications. [41]

Applications of Solid Dispersions:

Apart from absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications, which should be further explored,[42]

1)To obtain a homogeneous distribution of a small amount of drug in solid state.

2) To stabilize the unstable drug.

3) To dispense liquid or gaseous compounds in a solid dosage.

4) To formulate a fast release primary dose in a sustained release dosage form.

5) To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.

6) To reduce pre systemic inactivation of drugs like Morphine and Progesterone. Polymorphs in a given system can be converted into isomorphism, solid solution, eutectic or molecular compounds.

7) To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption and bioavailability.

8)To stabilize unstable drugs against hydrolysis, oxidation, recemization, isomerisation, photo oxidation and other decomposition procedures.

9)To reduce side effect of certain drugs.

Conclusion:

A significant obstacle in pharmaceutical research is the solubility of poorly water-soluble medications, which has a direct impact on their clinical effectiveness and bioavailability. Solid dispersion has emerged as one of the most successful and adaptable methods among the several created to address this problem. Solid dispersions provide notable improvements in medication dissolution and absorption patterns through a variety of production techniques and the use of different polymeric carriers. Their development into more sophisticated generations that include controlled-release polymers and surfactants highlights their increasing significance in contemporary drug delivery systems. Expanding the use of solid dispersions and eventually enhancing the therapeutic efficacy of difficult medication candidates are potential outcomes of ongoing research and innovation in this field.

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