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Review Article

Solubility Enhancement of Poorly Water- Soluble Drugs Using Solid Dispersion Method: A Review

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Abstract:

Solid dispersions have generated substantial attention as a technique of increasing the dissolution rate and hence the bioavailability of a variety of medications that are poorly soluble in water. Today, the pharmaceutical industry discovers up to 40% of novel chemical entities that are poorly soluble or lipophilic. Solid dispersions of insoluble in water pharmaceuticals in water-soluble carriers significantly minimise the occurrence of these difficulties and improve dissolution. Solid dispersion is one of the most promising methods for increasing solubility. The phrase "solid dispersion" refers to a collection of solid goods that have at least two distinct components, most often a hydrophilic matrix and a hydrophobic medication. The matrix might be crystalline or amorphous in nature. Class II medicines with limited solubility and high permeability are attractive candidates for bioavailability enhancement by solid dispersion, according to the biopharmaceutical categorization system. The purpose of this paper is to explore current achievements in the field of solid dispersion.

Keywords: Solid dispersions, solubility, carrier, Biopharmaceutical classification system.

Introduction:

The term 'solubility' refers to the highest concentration of a solute that may be dissolved in a given quantity of solvent. Solubility may be described qualitatively as the spontaneous interaction of two or more substances that results in the formation of a homogeneous molecular dispersion. Although theoretical prediction of accurate solubilities is a time-consuming and sometimes fruitless task, an informed judgment may be made based on information about the structure and characteristics of the solute and solvent. This is best represented subjectively, for example, as 'very soluble' or 'scarcely soluble'. Often (especially during the pre- or early stages of formulation), this is all the information required for the formulator.[1]

BCS Classification[2,3]:

Table 1: BCS Classification

BCS Class	Solubility	Permeability	Oral Dosage Form Approach
I	High	High	Simple solid oral dosage form
II	Low	High	Techniques to increase surface area like particle size reduction, solid solution, solid dispersion Solutions using solvents and or Surfactants
III	High	Low	Incorporate permeability enhancers, maximize local luminal concentration
IV	Low	Low	Combine 1 and 2

Class I: High permeability, high solubility
These types of drugs dissolve or absorbed and their therapeutic rate is usually higher than excretion.

Class II: High permeability, Low solubility

The bioavailability of class II drugs is limited by their solvation on rate. A correlation between the in vivo bioavailability and in- vitro solvation can be found.

Class III: Low permeability, high solubility

The absorption of class III category drug is limited by the permeation rate, but the drug dissolved very fast. If the formulation does not change the permeability or gastrointestinal duration time, then class l criteria can be applied.

Class IV: Low permeability, low solubility

The bioavailability of class IV category class is very poor. Usually they are not well absorbed over the intestinal mucosa due to their poor solubility. The drug has no IVIVC can be expected.[4]

Techniques for solubility enhancement:

Followings techniques are employed to improve solubility:

A. Physical Modifications

B. Chemical Modifications

Miscellaneous Methods

The phrase "solid dispersion" refers to a collection of solid goods that have at least two distinct components, most often a hydrophilic matrix and a hydrophobic medication. The matrix might be crystalline or amorphous in nature. The drug may be spread molecularly, amorphously (in clusters), or crystallinely.[5]

Enhancing the oral bioavailability of medicines that are poorly water soluble remains one of the most difficult elements of medication development. Although salt creation, solubilization, and particle size reduction have been often utilised to accelerate dissolving and boost bioavailability. The solubilization of pharmaceuticals in organic solvents or aqueous media by the application of surfactants and cosolvents results in liquid formulations that are often unfavourable from the patient acceptability and marketing perspectives. [6, 7]

As a result, solid dispersion technologies have the potential to significantly improve the oral absorption and bioavailability of BCS Class II medicines.

Types of Solid Dispersions:

Solid dispersions are of followings types:

A) Simple Eutectic Mixture
B) Amorphous solid solutions
C) Glass solutions and glass suspension
D) Solid solution
E) Continuous solid solutions
F) Discontinuous solid solutions
G) Subsitutional solid dispersions
H) Interstitial solid solutions

(A). **Simple Eutectic Mixture:** A eutectic combination of a medication with a low water solubility and a highly water soluble carrier may be seen thermodynamically as an intimate physical mixing of its two crystalline components. Typically, these systems are created by the melt fusion process. When the eutectic combination is exposed to water, the soluble carrier dissolves, exposing the medication in a microcrystalline form that is immediately soluble. Enhanced surface area is primarily responsible for the increased dissolving rate.[8]

(B). **Amorphous solid solutions:** Amorphous solid solutions include solute molecules that are molecularly dispersed but irregularly distributed inside the amorphous solvent.

(C). **Glass solutions and glass suspension:** A glass solution is a homogeneous solution in which the solute dissolves completely in the glassy solvent. Below the glass transition temperature, the glassy state is characterised by transparency and brittleness. Glass is a word that refers to a pure chemical or a combination of pure substances that is in its glassy condition. [(11)]

(D). **Solid solution:** Solid solutions, like liquid solutions, consist of a single phase regardless of the number of constituents. In the case of solid solutions, the particle size of the drug has been reduced to its molecular dimensions, and the dissolving rate is governed by the carrier's dissolution rate. Classified first according to their miscibility (continuous vs discontinuous solid solutions), and then according to the distribution

of the solvate molecules in the solvent (substitutional, interstitial or amorphous).

(E). **Continuous solid solutions:** The components of a continuous solid solution are miscible in all amounts. This implies that the bonding strength between the two components is greater than the bonding strength between the molecules of each component separately. Until yet, no solid remedies of this sort have been documented in the pharmaceutical sector.

(F). **Discontinuous solid solutions:** In discontinuous solid solutions, each component's solubility in the other component is restricted. The phrase "solid solution" should be used only when the mutual solubility of two components is more than 5%.

(G). **Subsitutional solid dispersions:** Substitution is achievable only when the size of the solute molecules is less than or equal to around 15% of the size of the solvent molecules. Classical solid solutions have a crystalline structure in which the solute molecules may either replace the solvent molecules in the crystal lattice or fit between the solvent molecules.

(H). **Interstitial solid solutions:** In interstitial solid solutions, the dissolved molecules fill the interstitial gaps in the crystal lattice between the solvent molecules. The diameter of the solute molecule should be less than 0.59 times that of the solvent molecule.[9]

Methods for preparation of solid dispersion:

A) Fusion method

B) Hot melt extrusion method

C) Solvent method

D) Supercritical fluid method

E) Co-precipitation method

F) Dropping method

G) Spray-drying

H) Kneading Technique

I) The use of surfactant

J) Electrospinning

(A). Fusion Method: The melting or fusion method, first proposed by Sekiguchi and Obi involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. Appropriately this has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate.[10]

(B). Hot melt extrusion method: This approach is identical to the fusion process except that the extruder does the vigorous mixing. This process use either twin crew extruders or a single extruder. This process enables the heated mixture to be shaped into implants, implant inserts, and oral dose forms. The solubility characteristics are researched in order to determine the solid state solubility and to pick a matrix appropriate for melt extrusion. Increased shear forces resulting in an increase in extruder temperature may provide a challenge for heat-sensitive materials.[11]

(C). Solvent method: In this method, the carrier and the active ingredients are dissolved in suitable organic solvent. The second step involves the removal of solvent(s) under vacuum.

(D). Supercritical fluid method: In this method carbon dioxide is used either as solvent for drug and polymer or as an anti-solvent. When carbon dioxide is used as a solvent, the solution mixture of carbon dioxide with drug and polymer is sprayed through nozzle into an expansion vessel with lower pressure and resulting in formation of particles. As this techniques does not involve use of any organic solvent termed as “Solvent free technique” and also known as Rapid Expansion of Supercritical Solution (RES).[12]

(E). Co-precipitation method: Co-precipitation is a well-established approach for improving the solubility of pharmaceuticals that are poorly soluble in water, hence boosting their bioavailability. Under continual stirring, non-

solvent is added drop by drop to the medication and carrier solution. The medication and carrier are co-precipitated to create microparticles during the non-solvent addition. Finally, the filtered and dried micro particle suspension is obtained. After mixing the needed amount of polymer and medication, solvent was added to generate a clear solution. The solution was first dried at ambient temperature under vacuum and then maintained in an incubator (37°C) for 12 hours. Finally, sieves were used to strain it.[13]

(F). Dropping method: This technique may overcome some of the difficulties inherent in the other method and developed to facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions. A solid dispersion of a melted drug carrier mixture is pipetted and then dropped on to a plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. The dropping method does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation.

(G). Spray-drying: Spray-drying is one of the most commonly used solvent evaporation procedures in the production of solid dispersions. It consists of dissolving or suspending the drug and carrier, then spraying it into a stream of heated air flow to remove the solvent. Due to the large specific surface area offered by the droplets, the solvent rapidly evaporates and the solid dispersion is formed within seconds, which may be fast enough to prevent phase separation. [14]

(H). Kneading Technique: In this method, carrier is permeated with water and transformed to paste. Drug is then added and kneaded for particular time. The kneaded mixture is then dried and passed through sieve if necessary.[15]

(I). Use of surfactant: The utility of the surfactant systems in solubilization is well known. Adsorption of surfactant on solid surface can modify their hydrophobisity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, solubilization, detergency, enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of investigators for preparation of solid dispersions.[16]

(J). Electrospinning: Electrospinning is a manufacturing method that produces solid fibres from a polymeric fluid stream solution or melt supplied via a millimetre-scale nozzle. A high electrostatic field is applied across a conducting capillary connected to a reservoir holding a polymer solution or melt and a conductive collecting screen. Charge species accumulating on the surface of a pendant drop collapse the hemispherical form into a conical shape when the electrostatic field intensity is increased up to but not surpassing a critical threshold (commonly known as Taylor s cone). When the critical value is exceeded, a charged polymer jet is expelled from the cone's apex (as a way of relieving the charge built-up on the surface of the pendant drop). The electrostatic force then carries the expelled charged jet to the collecting screen. Coulombic repulsion is responsible for the charged jet's thinning on its path to the collecting screen. The charged jet's thinning is restricted by the increased viscosity as it dries. This technology offers enormous promise for the manufacture of nanofibres and for regulating the release of medicines, since it is the easiest and least expensive. In the future, this technique may be used to prepare solid dispersions.[17]

Advantages of Solid Dispersion:

1. Solid dispersions are used for the improvement of the bioavailability of poorly water soluble drugs by enhance the dissolution of the drug.
2. Solid dispersions are better than other particle size reducing techniques to enhance the solubility,

because the other size reduction techniques reduces the size to a limit approximately 2-5 microns which doesn't cause enough enhancement in drug solubility or drug release in the small intestine and to improve the bioavailability.

3. Reduce pre-systemic metabolism, this may be due to carrier inhibit the enzyme responsible for biotransformation of the drug.
4. Liquid form of the drug can be transformed to solid form.
5. The problems of solid powder such as less size of particles shows poor mechanical properties (include high adhesion and poor flow properties) can be overcome by the use of solid dispersions.

Disadvantages

1. Amorphous state of a drug may undergo crystallization.
2. Aging may decrease the dissolution rate and changes in crystallinity.
3. Solid dispersions may be deteriorated in presence of moisture and excessive temperature.
4. The presence of moisture influences the crystallinity of the drug and stability issues are complicated. Some polymers used in solid dispersion are hygroscopic in nature and may absorb moisture that may result in the crystal growth. Sometimes the metastable form of drug may be changed to stable form. Hence, there may be a decrease in solubility and dissolution rate.
5. It is also difficult to understand the relation between structure of drug and its release from solid dispersion.
6. Difficulty in understanding the physical structure of solid dispersions.
7. Problem of residual solvents.
8. Prediction of shelf life of amorphous materials is difficult.

Applications of Solid Dispersion:

1. To obtain a homogeneous distribution of a small amount of drug.
2. To stabilize the unstable drug.
3. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
4. To formulate a fast release primary dose in a sustained released 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.
7. Polymorphs in a given system can be converted into isomorphous, solid solution, eutectic or molecular addition compounds.
8. Improve exposure (increase bioavailability, more rapid onset, decrease dose)
9. Reduce variability.[18]

Future Prospects

Despite the many benefits of solid dispersion, challenges with preparation, repeatability, formulation, scaling up, and stability have restricted its usage in commercial dosage forms for medications that are poorly water soluble. Recent years have seen the successful development of solid dispersion systems for preclinical, clinical, and commercial applications enabled by the availability of surface-active and self-emulsifying carriers with low melting temperatures. Dosage forms are prepared by dissolving the medicine and carriers in a solvent and then putting them into firm gelatin capsules or compressing them into tablets. Due to the ease of manufacturing and scaling up methods, the physicochemical characteristics of solid dispersions are unlikely to change dramatically throughout the scaling process. As a result, the solid dispersion system's appeal as a means of resolving tough bioavailability difficulties associated with weakly water-soluble pharmaceuticals will expand fast. Due to the fact that the dosage form can be developed and prepared using small amounts of drug substances during the early stages of the drug development process, the system may have an advantage over other commonly used bioavailability enhancement techniques, such as microionization and lyophilization. The discovery of novel surface-active and self-emulsifying carriers for solid dispersion will

be a key focus of future research. Currently, only a few of these carriers are accessible for oral usage.

Conclusion

Solubility is a critical factor in determining the oral bioavailability of insoluble medicines. Dissolution of the drug is the rate-determining phase in the oral absorption of medications that are poorly soluble in water, which may have an effect on the drug's in vivo absorption. Only 8% of novel medication candidates now have both good solubility and permeability. Due to the solubility issue with many medications, their bioavailability is compromised, and hence solubility augmentation becomes important. Solid dispersion technology is one method for increasing the solubility of pharmaceuticals that are poorly soluble.

The numerous technologies presented have shown success in both the laboratory and at scale. Certain items have been promoted utilising surface-active carrier technology. As a result, these technologies are likely to serve as a foundation for the commercialization of a large number of weakly water-soluble and water-insoluble pharmaceuticals in their solid-distribution formulations in the near future. Solvent systems composed of solvent mixtures may be utilised to improve solution concentration. Processing factors have an effect on the kind of glass amorphous system created.

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