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Review Article

Solubility Enhancement by Solid Dispersion Method: An Overview

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A B S T R A C T

To improve dissolution of poorly water-soluble drugs and thus enhancing their bioavailability, the dispersion of one or moreactive pharmaceutical ingredient in a carrier at solid state is used. This process is known as solid dispersion. It has engrossed significant interest as an efficient means of improving the dissolution rate. It happens due to dispersions of poorly water-soluble drugs with water-soluble carriers. The one of the most challenging aspects in formulation development is solubility behaviour of drugs. The number of poor water-soluble compounds has radically increased. Compared to conventional formulations such as tablets or capsules, solid dispersions prepared by various methods can be used which have many benefits over the above conventional dosage form. For the preparation of solid dispersions, few of the aspects are to be considered such as; selection of carrier and methods of physicochemical characterization. In this review, an emphasis is put on solubility, various types of solid dispersions, BCS classification, carriers, solid dispersion techniques, mechanism to enhance dissolution in solid dispersion, characterization, advantages, disadvantages and the application of the solid dispersions.

Keywords: Solubility, Solid Dispersion, Carrier, Bioavailability.

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INTRODUCTION

The Biopharmaceutical Classification System (BCS) divides drugs into four subclasses based on their solubility and permeability. While oral administration is the most common method of administering drugs to patients, many drugs have limited use in oral administration due to their poor solubility, which has a significant impact on their dissolution rate and bioavailability. Drugs in BCS classes II and IV have poor solubility, which is one of the most difficult challenges in improving the. Various techniques are employed for this goal, including solid dispersion, particle size reduction (Micronization and Nanonization), salt production, pH adjustment, polymorph and pseudo polymorph formation, complexation, and the use of surfactant and co-solvent. However, among these procedures, solid dispersion is the simplest and produces the most accurate results for increasing solubility [1].

Solubility

Solubility can be defined in two ways: quantitatively as the concentration of a solute in a saturated solution at a specific temperature, and qualitatively as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion [2].

Process of Solubilization[3]

***Step 1*:** The process of solubilization involves the breaking of interionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, the interaction between the solvent and the solute molecule or ion.

***Step 2*:** Molecule of the solid breaks away from the bulk.

***Step 3*:** The feed of a solid molecule is integrated into the hole in Solvent.

The US Food and Drug Administration (FDA) created the biopharmaceutics classification system (BCS), which divides drugs into four classifications based on their permeability and solubility. Solubility obstacle occurs in Class II and Class IV of the system, where dissolution is the rate-limiting stage for drug absorption due to its low solubility. The BCS classification system is described in Table No. 2.

Table 1: Definitions of Solubility

Definition	Parts of solvent required for one part of solute
Verysoluble	Lessthan1
Freelysoluble	From1 -10
Soluble From	From10 -30
Sparingly soluble	From30-100
Slightly soluble	Form 100-1000
Very slightly soluble	From1000 -10,000
Insoluble	Greater than 10,000

Table 2: The Biopharmaceutics Classification System for Drugs [4].

Class	Solubility	Permeability	Absorption Pattern	Rate limiting step in the absorption
I	High	High	Well absorbed	Gastric emptying
II	Low	High	Variable	Dissolution
III	High	Low	Variable	Permeability
IV	Low	Low	Poorly absorbed	Case by case

SOLID DISPERSION

Solid dispersion refers to a class of solid products that have at least two separate components, often a hydrophilic matrix and a hydrophobic medication. The matrix could be either crystalline or amorphous. The medication can be spread molecularly, in amorphous clusters, or as crystalline particles [5].

Mechanism responsible for solubility enhancement from solid dispersion

A variety of approaches can be used to improve the solubility and bioavailability of a poorly water-soluble medication.

- Reduced particle size:
- When the solid dispersion is subjected to watery fluids, the carrier dissolves and the medication is released as small colloidal particles. The increased surface area leads in a faster dissolving rate for low water-soluble medicines.
- Drug in amorphous state:
- Poorly water-soluble crystalline medicines in their amorphous state have a higher solubility. This is due to the fact that breaking the crystal lattice in an amorphous form during dissolution does not need any energy.

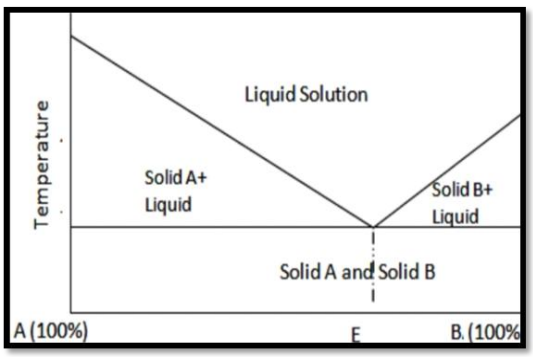

Figure 1: Phase diagram for eutectic mixtures

Amorphous precipitation in crystalline matrix

This is similar to simple eutectic mixtures; the only difference is that the drug precipitates out in an amorphous form [8].

- Particles with high porosity:
- Particles in solid dispersion have been found to have high porosity, which hastens the drug release profile. The increase in porosity depends on the carrier properties, with linear polymers producing larger and more porous particles than reticular particles.
- Particles with improved wettability:
- The improvement of drug wettability has been shown to have a significant impact on drug solubility in solid dispersion. Carrier with surface activity, such as cholic acid and bile salt, can greatly increase the wettability of the medication, resulting in an improved dissolving profile [6].

TYPES OF SOLID DISPERSION

Eutectic mixtures:

A simple eutectic combination is made up of two compounds that are totally miscible in liquid form but only partially so in solid form. It is created by rapidly solidifying a fused melt of two components that exhibit total liquid miscibility but negligible solid-solid solution [7].

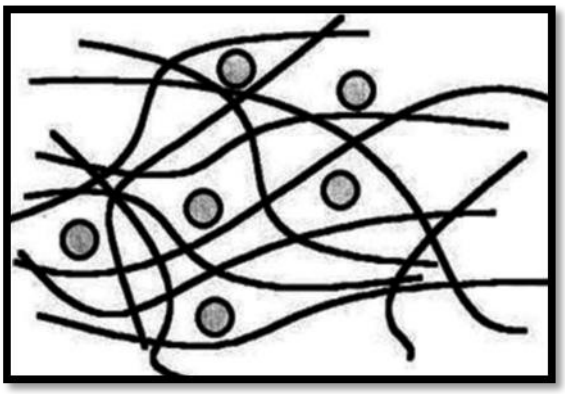

Figure 2: Amorphous solid Solution

Solid solution

Solid solutions, like liquid solutions, consist of only one phase, regardless of the number of components. In the case of solid solutions, the drug's particle size has been reduced to its

absolute minimum, referred to as molecular dimensions, and the dissolving rate is governed by the carrier's dissolution rate. They are classified first by their miscibility (continuous versus discontinuous solid solutions) and then by the distribution of the solvate molecules in the solvendum (substitutional, interstitial, or amorphous)[9].

Continuous solid solutions

In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each individual component. This type of solid solution has yet to be reported in the pharmaceutical industry.

Discontinuous solid solutions

In discontinuous solid solutions, the solubility of one component in the other is limited. Due to practical reasons, it has been proposed that the term 'solid solution' be used only when the mutual solubility of the two components surpasses 5% [10].

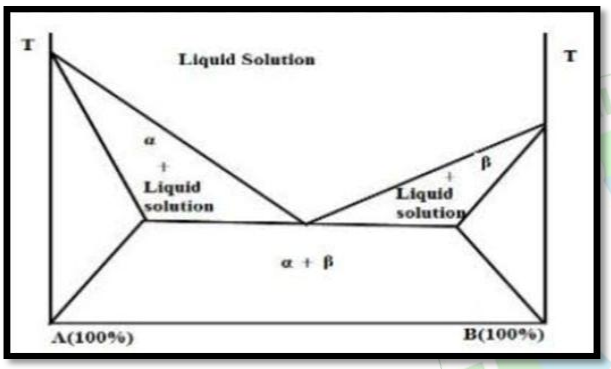

Figure 3: Phase diagram for discontinuous solid solutions

Substitutional solid dispersions

Classical solid solutions have a crystalline structure, and the solute molecules can either substitute for the solvent molecules in the crystal lattice or fit into the interstices between the solvent molecules[11]. Substitution is only possible when the size of the solute molecules differs by less than 15% from that of the solvent molecules.

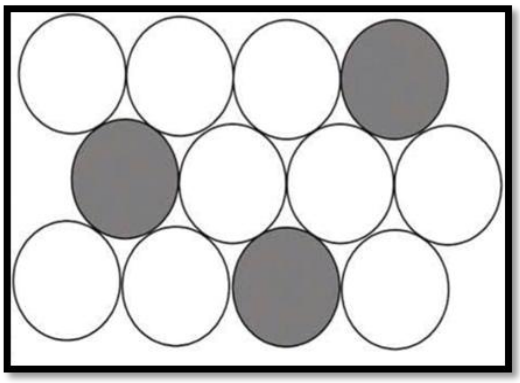

Figure 4: Substitutional crystalline solid solutions

Interstitial solid solutions

In interstitial solid solutions, the dissolved molecules fill the interstitial spaces between the solvent molecules in the crystal lattice. The diameter of the solute molecules should be smaller than 0.59 times the diameter of the solvent molecules.

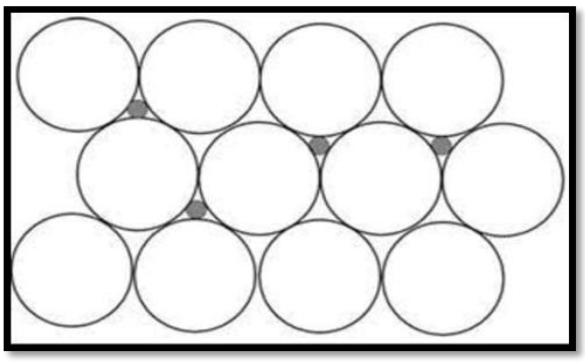

Figure 5: Interstitial crystalline solid solutions

Glass solution and suspensions

Glass solutions are homogenous glassy systems in which solutes dissolve in a glass carrier. Glass suspensions are mixtures composed of precipitated particles suspended in a glass solvent. Lattice energy is significantly lower in glass solution and suspension [9].

Advantage of Solid Dispersion

- Improve wettability.
- Improve drug porosity.
- Transform pharmaceuticals from crystalline to amorphous.
- To conceal the flavour of the psychoactive substance.
- Prepare oral tablets with fast breakdown.

Disadvantages of Solid Dispersion

- Moisture and temperature have a greater negative impact on solid dispersion than physical combination.
- Tackiness can make handling difficult.
- Reproducibility of physicochemical attributes.
- Formulated into dose forms[12]

Selection of A Carrier

A carrier should match the following criteria to be suitable for boosting the dissolving rate of a medication.

- Freely water-soluble with fast dissolution.
- Non-toxic and pharmacologically safe.
- Suitable for the melt process because to its low melting point and heat stability.
- Soluble in various solvents and becomes vitreous upon evaporation using the solvent technique.
- Improves medication aqueous solubility.
- Compatible with the medication and does not generate a strong complex [13].

First Generation Carrier

In the first generation, solid dispersion, eutectic mixture formulation, or molecular dispersion improved drug release rates, increasing the bioavailability of weakly water-soluble medicines. The crystalline solidformulationhas the disadvantage of slowing medication release. Crystalline carriers include urea, sugars, and organic acids.

Second Generation Carrier

In the second generation, we use amorphous carriers to increase drug release; fully synthesized polymers include povidone (PVP), polyethylene glycols (PEG), and polymethacrylates. Natural product-based polymers are mostly made up of cellulose derivatives such as hydroxypropyl methylcellulose (HPMC), ethyl cellulose, and hydroxypropyl cellulose, as well as starch derivatives such as cyclodextrins[14].

Third Generation Carrier

In the third generation, we use carriers that have surface activity and self-emulsifying capabilities. Surfactants inhibit medication recrystallization, hence enhancing solubility. Poloxamer 408, Tween 80, and Glacier 44/141 are surface active self-emulsifying carriers[15].

SELECTION OF SOLVENTS

The solvent to be included in the formulation of solid dispersion should meet the following criteria:

- The medication and carrier must be dissolved.
- Avoid using toxic solvents like chloroform and dichloromethane since they may leave residual quantities after preparation.
- Ethanol is a safer option.
- Water-based systems are ideal.
- Surfactants can reduce glass transition temperature; thus, caution should be exercised when using them in carrier drug solutions[16].

METHOD OF PREPARATION OF SOLID DISPERSION

Melting Method

The melting or fusing approach, first proposed by Sekiguchi and Obi, entails preparing a physical mixture of a medication and a water-soluble carrier and directly heating it until it melts. The melting slurry is then quickly solidified in an ice bath while vigorously churning. The resulting solid mass is crushed, pulverized, and sieved. This has undergone various changes, including pouring the homogeneous melt in the form of a thin layer onto a ferrite or stainless-steel plate and cooling it with flowing air or water on the opposite side of the plate. Furthermore, super-saturation of a solute or medicine in a system can frequently be achieved by fast quenching the melt at a high temperature. Under those conditions, the immediate solidification process arrests the solute molecule in the solvent matrix. When used to simple eutectic mixtures, the quenching approach results in substantially finer crystallite dispersion[17].

Solvent Evaporation Method

The solvent evaporation method involves solubilizing the medication and carrier in a highly volatile solvent, which is then evaporated. Because organic solvent evaporation occurs at low temperatures, this approach frequently avoids the heat destruction of drugs or carriers. The basic method for generating solid dispersions of this type is to dissolve the medication and its polymeric carriers in a common solvent, such as ethanol, chloroform, or a combination of ethanol and dichloromethane. Typically, the resultant films are pulverized and milled [18].

Melting Solvent Method (Melt Evaporation)

Solid dispersions are prepared by dissolving the medicine in a suitable liquid solvent and then integrating the solution directly into a polyethylene glycol melt, which is subsequently evaporated until a clear, solvent-free film remains. The film is subsequently dried to a consistent weight. Polyethylene glycol6000 may include 5-10% (w/w) liquid substances without significantly affecting its solid properties37. The specified solvent or dissolved medication may not be miscible with the polyethylene glycol melt furthermore, the liquid solvent utilized may influence the polymorphic form of the drug, which precipitates as a solid dispersion. This process has distinct advantages over both the fusion and solvent evaporation methods. From a practical sense, it is only applicable to medications with a low therapeutic dose, such as less than 50 mg[19].

Melt Extrusion Method

A twin-screw extruder is commonly used to process the drug/carrier mixture. The drug/carrier mixture is melted, homogenized, and then extruded and moulded into tablets, granules, pellets, sheets, sticks, or powders. The intermediates can then be further treated to produce regular tablets. A significant advantage of the hot melt extrusion method is that the drug/carrier mix is only exposed to elevated temperatures for about 1 minute, allowing pharmaceuticals that are slightly heat labile to be treated. This approach produces solid dispersion from active ingredients and carriers using hot-stage extrusion with a co-rotating twin-screw extruder. The medication content in the dispersions is consistently 40% (w/w). The screw configuration consists of two mixing zones and three transport zones that are distributed across the full barrel length; the feeding rate is fixed at 1 kg/h, and the screw rate is set at 300 RPM. From feeder to die, the five temperature zones are adjusted to 100, 130, 170, 180, and 185°C. After cooling to ambient temperature, the extrudates are collected on a conveyer belt. Samples are milled for 1 minute using a laboratory-cutting mill and sieve to remove particles larger than 355µm [28].

Lyophilization Technique

Freeze-drying involves the transfer of heat and mass to and from the product being prepared. This technique was suggested as an alternative to solvent evaporation. Lyophilisation has been described as a molecular mixing procedure in which the drug and carrier are co-dissolved in a shared solvent, frozen, then sublimed to produce a lyophilized molecular dispersion[20].

Kneading Method

A mixture of medication and polymer was wetted with water and thoroughly kneaded in a glass mortar for half an hour. The paste is then dried under a vacuum for 24 hours. The dried powder is sieved 60 times and stored in desiccators awaiting further assessment[21].

Co-Grinding Method

A physical mixture of medicine and carrier is combined several times with a blender set at a specific speed. The powder combination is crushed. The blend is then charged into the office of a vibration ball manufacturer, which

includes steel balls. The powder composition is pounded. The sample is then collected and stored at room temperature in a screw-capped glass vial until ready for use. For example, this approach was used to make chlordiazepoxide solid dispersion[23].

Spray Drying Method

The drug is dissolved in a suitable solvent, and the necessary amount of carrier is dissolved in water. The solutions are then mixed by sonication or another suitable method to provide a transparent solution, which is evaporated under a vacuum. Solid dispersions are reduced in size by mortar and sieved[24, 29].

Melt Agglomeration Process

A rotary processor has been shown to be an alternative equipment for melt agglomeration. This technique has been used to prepare SD wherein the binder acts as a carrier. Additionally, SD(s) is prepared either by heating the binder, drug, and excipient to a temperature above the melting point of the binder (melt-in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray-on procedure) using a high shear mixer.The effect of binder type, manufacturing process, and particle size are essential parameters in the preparation of SD(s) via melt agglomeration. These characteristics cause changes in dissolution rates, agglomeration formation and growth mechanisms, agglomerate size, agglomerate size distribution, and agglomerate densification. The melt-in approach has been shown to have a higher dissolution rate than the spray-on procedure with PEG 3000, poloxamer 188, and glacier 50/13, which is due to the immersion process of agglomeration creation and growth. Furthermore, the melt in method ensures that the medication is distributed uniformly throughout the agglomeration.Larger particles induce agglomerates to densify, but fine particles cause total adherence to the mass to the bowl quickly after melting, which can be attributed to fine particle distribution and coalescence [25].

Electrospinning

Electrospinning is the process of producing solid fibres from a polymeric fluid stream solution or melt fed through a millimetre-scale nozzle. A high electrostatic field is applied across a conducting capillary that is connected to a reservoir containing a polymer solution or melt, as well as a conductive collection screen. When the electrostatic field strength reaches but does not exceed a certain value, charge species build on the surface of a pendant drop, destabilizing the hemispherical shape into a conical shape (often known as Taylor's cone). Beyond the critical value, a charged polymer jet is blasted from the cone's apex (to relieve the charge on the pendant drop's surface). The ejected charged jet is then transported to the collection screen by electrostatic force. The Coulombic repulsion force causes the charged jet to narrow out as it approaches the collection screen. The thinning of the charged jet is restricted by the increase in viscosity as it dries. This technology has enormous potential for the manufacture of nanofibers and controlling the release of biomedicine; because it is the simplest and cheapest, it can be used to prepare solid dispersions in the future[26].

Applications of The Solid Dispersion

- Solid dispersion systems can provide bio-available oral dosage forms for anti-cancer drugs, improving patient compliance and comfort. They also serve as functional carriers, releasing highly soluble forms of poorly water-soluble drugs to optimal sites for absorption.
- The solid dispersion systems were also discovered to lessen the effects of food on medication absorption, hence boosting the convenience of drug therapy by eliminating the need to take some pharmaceuticals with food.
- Solid dispersion formulations have been shown to speed up the onset of action for medications like NSAIDS, which require fast relief from pain and inflammation.
- Solid dispersion methods enhance absorption efficiency, reducing the amount of active agent required per dosage and lowering costs for medication regimens.
- A dry powder formulation with solid dispersion for inhalation improves immunosuppressive therapy in lung transplant patients. Many difficulties can be avoided, including the use of local anaesthesia and irritant solvents[27, 30].

CONCLUSION

The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Dissolution of drug is the rate determining step for oral absorption of drugs, which can subsequently affect the in vivo absorption of drug. Because of solubility problem of many drugs the bioavailability of these gets affected and hence solubility enhancement becomes necessary. Soliddispersions are one of the most attractive processes to improve drug's poor water solubility. Various solubility enhancers like water-soluble carriers, co solvents, surfactants and superdisintegrants via solid dispersion approach (fusion method and solvent evaporation method) aids in solubility enhancement. These significantly help to improve the bioavailability and bioequivalence.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

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