SOLID DISPERSION: TYPES AND MECHANISM OF SOLID DISPERSION-BASED SOLUBILITY IMPROVEMENT

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Abstract: The dispersion of one or more active pharmacological ingredients in a carrier at solid state is used to increase the dissolution of poorly water-soluble remedies and hence enhance their bioavailability. Solid dispersion is the name of this procedure. It has drawn a lot of attention as a practical way to raise the disintegration rate. It occurs because weakly water-soluble medicines are mixed with water-soluble carriers. The solubility behaviour of pharmaceuticals is one of the most difficult formulation development issues. Poorly water soluble chemicals have dramatically risen in number. Solid dispersions created using various techniques can be utilised as an alternative to typical formulations like tablets or capsules and have many advantages over the aforementioned conventional dosage form. A few aspects must be considered when preparing solid dispersions, such as vehicle for change and physicochemical characterisation methods. This review focuses on solubility, different types of solid dispersions, BCS categorisation, carriers, solid dispersion techniques, mechanism to enhance dissolution in solid dispersion, categorisation, benefits, drawbacks, and solid dispersion applications. The current review focuses on how solid dispersions are portrayed, along with their types, which include eutectic mixtures and solid solutions, preparation methods, and helpful carriers.

Keywords: Solid dispersion, carrier, bioavailability, and solubility

INTRODUCTION:
A drug is absorbed by the oral route when it dissolves from the formulation into the stomach and/or intestinal fluids, permeates the gastrointestinal cell membranes, and then enters the bloodstream. One of the most popular formulation types is oral solid dose forms, which has many advantages over other formulations/routes. The difficulty for a pharmaceutical scientist, however, comes from the fact that a medication's water solubility is dependent on the drug's ability to dissolve from an oral solid formulation, which is a crucial aspect of drug absorption. Therefore, a medicine with poor water solubility would show restricted absorption due to dissolution rate, and a drug with poor membrane permeability would similarly show limited absorption due to penetration rate. A medication is highly soluble if its greatest dose dissolves in at least 250 ml of water with a pH range of 1 to 7.5, and it is highly permeable if human absorption is expected to be at least 90% of a dose that has been provided. According to research, the majority of newly discovered chemicals that are utilised as solid dosage forms should result in an effective and repeatable plasma concentration after oral administration. However, the majority of them have a poor water solubility, which reduces the drug's therapeutic effectiveness. Furthermore, poor solubility leads to greater doses and more frequent administration, which increases the likelihood of side effects. Therefore, pharmaceutical research has focused on increasing the solubility, rate of dissolution, and membrane permeability of weakly water-soluble drugs to increase their oral bioavailability. Drugs that are weakly soluble in water and highly permeable across biological membranes have been used extensively in research on solid dispersion approach because, in the case of these drugs, dissolution is the rate-limiting stage in absorption. In light of this, it has been expected that the rate of absorption will rise along with the rate of disintegration. Drugs classified as Class II drugs often have strong membrane permeability and low water solubility according to the Biopharmaceutical Classification System (BCS). In order to increase Class II medication bioavailability by oral absorption, the solid dispersion approach is specifically applied.
Poor aqueous solubility has been addressed using a variety of tactics, including chemical modification, changing the solvent's composition, using a carrier system, and physical modification, such as the solid dispersion approach. Solid dispersion technology, however, stands out from the competition as the most promising method for making poorly soluble drugs more soluble. When creating oral drug delivery systems, the ability to formulate poorly soluble medicines into solid dispersions opens up a wider range of processing and excipient possibilities. The creation of extended release dosage forms has been the focus of recent research on solid dispersion systems, in addition to improvements in solubility and bioavailability. Sekiguchi and Obi reported the eutectic mixture of sulfathiazole and urea’s synthesis in 1961 and showed that the substance was present in microcrystalline form\(^\text{[10]}\). The substance need not be in a microcrystalline form, according to another study; a portion of the drug could be molecularly diffused in the matrix and form solid solution\(^\text{[11]}\). Poorly water-soluble medications' bioavailability and dissolution rate are increased when a solid dispersion is dispersed in an aqueous medium, which is due to the carrier's solubilization and release of the drug as tiny colloidal particles\(^\text{[5]}\). This article provides a brief review on the types and characterization of solid dispersions, description of different generations, detailed research conducted on solid dispersion and also the challenges encountered in formulation development.

**SOLID DISPERSION:**

When compared to a liquid solution, a solid solution containing a medication that is weakly water-soluble or a solid solvent with a solid solute that is well-soluble in water can more effectively dissolve a drug. Single-phase solid solutions are the end product of two chemicals dispersing within one another at the molecular level\(^\text{[16]}\). The creation of a homogeneous single phase system is thus caused by the simultaneous crystallisation of both substances. Due to the fact that the drug particle size is lowered to the molecular level, solid solutions created by combining highly water soluble carriers with water insoluble carriers have the potential to have a superior dissolving rate than eutectic combinations. The size of the medium being.

**Solid Dispersions' Generational Breakdown:**

Solid dispersions can be divided into four generations based on their composition and processing.
Solid dispersions of the first generation:
First, a study by Sekiguchi and Obi gave rise to the term "solid dispersions," where a eutectic mixture was created to speed up the dissolving of water-insoluble treatments as well as their oral bioavailability. These solid dispersions, which were created using the crystalline carriers urea, sugars, and organic acids, were referred to as first generation solid dispersions. However, the construction of the first generation of solid dispersions was also linked to the development of crystalline solid dispersions, which, despite being thermodynamically stable, were unable to accelerate drug release as quickly as amorphous dispersions [6,10,14,17].

Solid dispersions of the second generation:
Amorphous carriers were introduced in the second generation of solid dispersions to replace crystalline ones. In this case, an amorphous polymeric carrier contains a molecularly distributed medication. These carriers, which may create amorphous solid dispersions and can be further classified into synthetic and natural product based polymers, were widely employed for solid dispersions. Polyethylene glycols, povidone, and polymethacrylates are examples of synthetic polymers. Natural polymers made up of various starch (sodium starch glycolate) or cellulose derivatives (ethylcellulose or hydroxypropylcellulose) [19-21].

Solid dispersions of the third generation:
In order to improve the dissolution more effectively, third generation solid dispersions use carriers with self-emulsifying capabilities or a combination of amorphous polymers and surfactants as carriers. These third-generation solid dispersions aim to stabilise the solid dispersion by preventing drug recrystallization as well as achieve extremely high bioavailability. The usage of carriers such Poloxamer 408, Tween 80, and Gelucire 44/14 is part of it [22-24].

Solid dispersion of the fourth generation:
In the fourth generation solid dispersion, sometimes referred to as controlled release solid dispersion (CRSD), we use medications with a limited biological half-life that are poorly water soluble. Solubility improvement and controlled extended release are two of its objectives. In this generation, drug solubility will be improved by molecular dispersion in a carrier, as opposed to drug release being slowed down by the usage of water-swellable polymers. Because of this, we are able to administer an adequate dose of medication for a prolonged period of time, which has a number of positive effects on patient compliance, reduced dosing frequency, fewer side effects, and prolonged therapeutic effect for medications with poor water solubility and short biological half-lives. Ethyl cellulose, hydroxypropyl cellulose, Eudragit RS, RL, poly (ethylene oxide), and carboxyvinyl polymer are among the polymers that are employed [25-26].
Solid Dispersion-Suitable Carriers:
As carriers for solid dispersions, many water-soluble excipients are used. The following are the considerations that should be made when choosing such carriers: High glass transition point improves stability; low water absorption reduces Tg; soluble in the same solvent as the medication (solvent evaporation); comparatively low melting point (melting process); and capable of creating a solid solution with solubility characteristics comparable to those of the drug.

Poloxamers:
Poloxamers are substances with surface activity that are frequently employed in the pharmaceutical sector. They are block polymers of the a-b-a type, which typically have a centre block of hydrophobic polypropylene oxide surrounded by two blocks of hydrophilic polyethylene oxide. Propylene oxide and ethylene oxide are sequentially polymerized to produce the polymers, and due to the possibility of combining blocks with various molecular weights, the polymers' characteristics vary greatly. Typically, they are waxy, white granules that flow freely and have no flavour or scent. They go by the name pluronics as well. The inclusion of metal ions, acids, and alkalis has no effect on the stability of pluronic aqueous solutions. Due to their free solubility in both polar and non-polar organic solvents, they have been regarded as a favoured molecule in the formulation development process. There are numerous alternative poloxamers with distinctly different characteristics since the lengths of the polymer blocks can be altered [27-28]. The initials “P” (for poloxamer) are followed by three digits, the first two of which are multiplied by 100 to give the approximation of the molecular mass of the polyoxypropylene core of the copolymer. The percentage polyoxyethylene content is also determined by multiplying the final digit by 10 (for instance, P407 is a poloxamer with a polyoxypropylene molecular mass of 4000 g/mol (40100) and a 70 percent (710) polyoxyethylene content).

Polyethylene glycol, (PEG): 
PEG is a common water soluble polymer that is formed by mixing ethylene oxide monomers, which typically have molecular weights between 200 and 300,000. PEGs having molecular weights between 1500 and 20,000 are typically used in the creation of solid dispersions and solutions. They cause an increase in viscosity as the molecular weight rises. One of the key elements that influences a solid dispersion's qualities is the drug to carrier ratio. The problematic PEGs have a melting point of under 65 degrees. By preparing their solid dispersion in PEG 6000, a number of water-insoluble medicines' rate of dissolution has been improved [29].

Polyvinylpyrrolidone (PVP):
Vinyl pyrrolidone is converted into PVP, which has molecular weights between 2500 and 30,000. PVPs have a limited use for making solid dispersions using the hot melt method, but they work well when making solid dispersions using the solvent approach because of their good solubility in a number of organic solvents. It has been shown that an enhanced solid dispersion in PVP has improved wettability and, consequently, improved dissolving rate. The fact that PVPs display poor aqueous solubility as chain length increases and much increased viscosity at a given concentration due to their large molecular weight is a serious drawback. This was found in the case of indomethacin where the slower dissolution of indomethacin was observed from PVP K90 compared to PVP K12. It was attributed to the higher viscosity generated by PVP K90 in the diffusion boundary layer adjacent to the dissolving surface of the dispersion. Similar to PEG, solid dispersions prepared with high proportions of PVP tends to high drug solubility and release rate than those with high proportions of drug. Most studies of PVP solid dispersions reported in the literature have used PVPs of molecular weight 2500±50 000 (K12 to K30) [30-31].

Copolymer of polyvinyl alcohol and polyvinylacetate (PVA)/PVP:
These polymers are water soluble and part of the polyvinyl group. It has been observed that using PVA/PVP copolymers as carriers in solid dispersions significantly increases the rate of medication release. When nicotinamide with PVP, hydroxypropylmethylcellulose (HPMC), or PVA were used as carriers to generate nifedipine dispersions, those made with PVA dispersed 20 times more quickly than those made with the drug alone. The outcomes from the other carriers, HPMC and PVP, were considerably better [30-31].

Crospovidone:
This polymer expands when distributed in water, and is a member of the polyvinyl group. Despite not dissolving in water, crospovidone can be employed as a carrier to increase the rate at which drugs are released from solid dispersions. For instance, compared to either the drug powder or the physical mixture of furosemide and crospovidone, solid dispersion of the two drugs increased the rate of dissolution by a factor of 5.8. According to X-ray diffraction investigations, the drug's amorphous form was present in the produced dispersion, which is what caused the rise in furosemide release rate [31].

Derivatives of cellulose, HPMC:
Natural polysaccharides called celluloses can be further derivatized to create various carriers. HPMC have a molecular weight range of 10,000–15,000 and are totally soluble in water. They are mixed cellulose ethers in which 4–32 percent of the hydroxyl groups are derivatized with hydroxypropyl groups and 16-30 percent of them are methylated. The release rate and bioavailability of albendazole were improved when HPMC was employed to prepare the solid dispersion. It was also discovered that HPMC might prevent albendazole from crystallising, and that combining HPMC and HPMCP could enhance release characteristics even more. Poorly soluble weak acids like nilvadipine and benidipine also show quicker release from solid dispersion in HPMC [32].

Hydroxypropylcellulose:
In addition to water (up to 408°), ethanol, methanol, and chloroform, hydroxypropylcellulose is also soluble. Between 37 000 (Type SSL) and 11 50 000, the hydroxypropylcellulose's average molecular weight is found (Type H). They are mixed cellulose ethers in which 4-32 percent of the hydroxyl groups are derivatized with hydroxypropyl groups and 16-30 percent of them are methylated. The release rate and bioavailability of albendazole were improved when HPMC was employed to prepare the solid dispersion. It was also discovered that HPMC might prevent albendazole from crystallising, and that combining HPMC and HPMCP could enhance release characteristics even more. Poorly soluble weak acids like nilvadipine and benidipine also show quicker release from solid dispersion in HPMC [32].

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Polyols, sugar, and their polymers:
Although having a lower level of toxicity and being highly water soluble, sugars and related chemicals are less effective than other carriers for the creation of solid dispersions. Due to their high melting point, sugars limit the use of the hot melt process for making solid dispersion. Similar to how it is difficult to create co-evaporates, it has poor solubility in the majority of organic solvents. Despite these limitations, there have been several attempts to prepare solid dispersions using sugars and their derivatives. One such example is mannitol, which has a melting point between 165 and 168°, only decomposes above 250°, and has occasionally been used to make dispersions using the hot melt method [34].

Techniques for Solid Dispersions:
Various methods of preparation solid dispersions are summarized as:
- Solvent evaporation
- Hot-melt extrusion
- Fusion method
- Solvent melt method
- Kneading technique
- Inclusion complexes
- Direct capsule filling
- Surface active carriers
- Particle size reduction
- Adsorption on insoluble carriers/fluidized bed system
- Solid deposition on super disintegrants
- Melt agglomeration method
- Dropping method

Different Methods of Preparation:

Kneading method:
When using the kneading method, water is added to the drugs and carrier to create a thick paste, which is then kneaded for a predetermined amount of time. To get a uniform size of solid dispersion, the kneaded material is dried and sieved [35].

Melting technique:
Using a mortar and pestle, the drug and carrier are thoroughly combined to create a homogeneous dispersion before the combination is heated above the melting points of the drug and carrier. After cooling, a hard mass is created, which is subsequently crushed and sieved to provide a uniform dispersion. However, this approach has a number of limitations because it is inappropriate for thermolabile medications and polymers with high melting points like PVP [14].

Method of co-precipitation:
In this procedure, a solution of the carrier is created, and the correct amount of drugs is added before being stirred magnetically. To encourage precipitation, an antisolvent is added to this. It is filtered, dried, and the precipitate is removed [35].

Co-grinding procedure:
The right quantity of drug and carrier are combined and ground in the chamber of a vibration ball using a blender operating at a specific speed. Strong grinding pressures cause crystal lattice deformation and raise activation energy. When the drug is processed in a vibrating ball mill with a carrier, the crystallinity of the drug is reduced, which increases the bioavailability and solubility rate [36].

Method of solvent evaporation:
In order to obtain solid mass, drug and carrier are dissolved in a typical organic solvent and evaporated. After that, the solid mass is crushed, sieved, and dried. The two key variables that affect the solid mass are the type of solvent and the temperature at which the solvent will evaporate. When drug and carrier are dissolved in a solvent and subjected to hot air flow in a spray dryer, the solvent is evaporated, changing the solvent evaporation method for the formation of solid dispersions. Similar to solvent evaporation,
freezedrying technology (lyophilization) involves dissolving the drug and carrier in a common solvent, which is then frozen and sublimed to produce a lyophilized molecular dispersion. Small changes in either method's solvent evaporation conditions have a noticeable impact on how well the result works. Given that the vast majority of organic solvents are connected to toxicity problems, even the utilised organic solvent should be carefully eliminated [14].

Method of electrostatic spinning:
With this technique, solid fibres with submicron diameters are created by passing a polymeric melt or solution through a millimeter-sized nozzle. Solid fibres are created as the solvent evaporates and can be gathered on a spinning mandrel. Electrostatic forces are involved in this process, which when they outweigh the surface tension of the solution at the air-liquid interface, result in the creation of fibres. The technique is easy, inexpensive, and has incredible potential for creating nanofibers and managing a drug's release [3].

Use of melt extrusion:
Using a spinning twin screw extruder, a medication and carrier mixture is extruded through in this method for making solid dispersion. The two crucial factors that influence how well solid dispersions perform are screw speed and water content. The drug concentration in the dispersions is kept at 40% w/w, and a plasticizer can be added to the extrudate at a concentration of between 5% and 30% weights to reduce the viscosity of the melt [37].

Process of melt agglomeration:
With this technique, the binder—which serves as a carrier, drug, and excipient—is heated above the binder's melting point. Additionally, it can entail utilising a high-shear mixer to spray the drug dispersion in molten binder onto the heated excipient. The rotary processor is an alternate piece of equipment for melt agglomeration due to superior temperature control and the high feasibility of binder content to be integrated in the agglomerates [38].

Process using supercritical fluid
This method can be used to create solid dispersions without the use of solvents. A substance that occurs above its crucial stage at a specific temperature and pressure is known as a supercritical fluid (SCF). The density of the liquid begins to decrease as it is heated, whilst the density of the vapour increases. There is no phase barrier as the critical point is reached, and the densities of both liquid and gas are equal [39]. The fluid has both the ability to penetrate and act as a solvent above this critical point (the supercritical region). In the SCF antisolvent technology, carbon dioxide is used as an antisolvent for the solute. and also precipitation from gassaturated solutions particles from gas saturated solutions (PGSS) [40].

Solid-Dispersions Characterization:
Solid dispersions may have a number of the drug's molecular structures in the matrix. Scientists have worked hard to distinguish between amorphous and crystalline materials, and they have also investigated how molecules are structured in solid dispersions. There are numerous approaches available to determine how much crystalline material is present in the dispersion. lists various techniques for characterising solid dispersions.

Despite the fact that solid dispersion has several benefits, the aforementioned factors restrict its application in pharmaceutical dosage forms. The use of traditional methods for creating solid dispersions is constrained by the numerous issues they provide. The melt technique processing parameters affect the stability and physicochemical characteristics of solid dispersions. The removal of all organic solvents employed during preparation is a challenging task. It is also difficult to produce solid dispersion dosage forms into tablets or capsules. These severe issues have been mentioned below. The soft and waxy character of the carriers used in the formation of solid dispersions also has some serious issues. Physical instability as a result of the amorphous state becoming crystalline during storage has an impact on dissolution characteristics and the bioavailability of drugs manufactured as solid dispersions. However, crystalline drugs nucleate and recrystallize in solid dispersions during storage [82]. The inability to scale up the solid dosage formulation from a small scale melt quench or a solvent-evaporation technique, a lack of understanding of the mechanism of drug dissolution from the dosage form, the prevention of some drugs' crystallisation in gastric fluids, and a lack of comprehension of the in vitro-in vivo correlation between these dosage forms are a few other pitfalls that also require in-depth studies.

Future Prospects:
Due to recent technological developments in the production process, scale-up, and development of fresh technologies for greater predictability of solid state structure, solid dispersions for poorly soluble drugs will shine. To overcome the difficulties in designing novel carriers that can prevent crystallisation of drug, future research on solid dispersions should employ new methodologies to examine the solubility and molecular state of the drug and its interaction with the polymer. More attention needs to be paid to how storage conditions affect drug characteristics, carriers used, drug release profiles, and drug bioavailability. Furthermore, it is conceivable that using a hydrophobic carrier instead of a hydrophilic one will produce a well-controlled solid dispersion process. The technique is simple to use to achieve drug sustained release or to change solid state features. It is crucial that the solid dispersion approach has enormous potential for future study and development, which could lead to the creation of new uses for oral medication administration. Last but not least, the question arises as to whether the use of solid dispersion technology may be regarded as an all-purpose strategy for improving the solubility of poorly water-soluble substances. Currently, not all medications and dosing requirements are compatible with all methods utilised to increase drug solubility in aqueous solutions. But there is still interest in figuring out how stable the amorphous form of solid dispersions is this demands the attention of scientists, and there is still work to
be done to fully reap the rewards of this potent method. The most adaptable method for improving poorly water soluble medication dissolution, however, is solid dispersion, which may be employed for the majority of compounds and their dosage requirements.

Strategies for overcoming common solid dispersions problems:
Polymers frequently have higher glass transition temperatures (Tg) than API, so they can reduce drug molecular mobility by increasing the Tg of the miscible mixture or interacting with drug molecules\(^{[86-87]}\). To prevent drug recrystallization, a polymer must be miscible with the drug, and the miscibility is determined by the chemical interactions between the drug and polymer \(^{[88-89]}\). The main force increasing solid miscibility and thus preventing phase separation and drug recrystallization is hydroxyl group between the drug and polymer. Many polymers, however, are hygroscopic, and water absorbed by polymers may increase molecular mobility. Furthermore, there are some common problems in the preparation, formulation and dissolution process that researchers have to consider in research and development of solid dispersion products. These problems include the thermal instability of drugs and carriers in the melting method, the solvent residue in the solvent method, the recrystallization of drugs in solidification and further formulation process, the low in vivo–in vitro correlation, and the precipitation of drugs after dissolving in water due to supersaturation.

References:


